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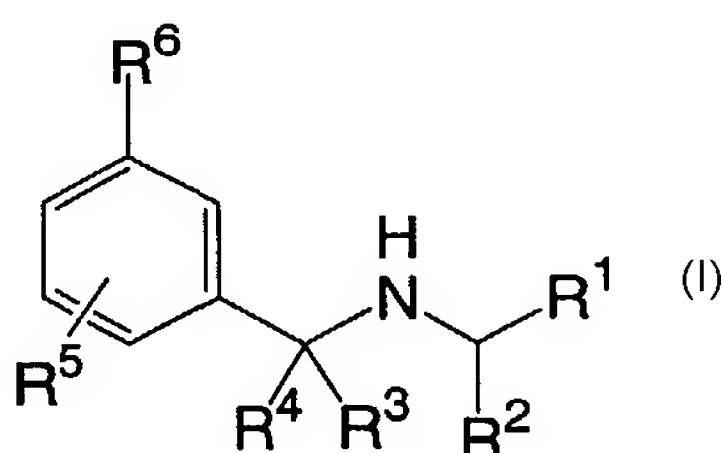
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(54) Title: CALCIUM RECEPTOR MODULATING ARYLALKYLAMINES



(57) Abstract: The compounds of the invention are represented by the following gen-  
eral structure (I) or a pharmaceutically acceptable salt thereof, and compositions con-  
taining them, wherein the variables are defined herein, and their use to reduce or in-  
hibit PTH secretion, including methods for reducing or inhibiting PTH secretion and  
methods for treatment or prophylaxis of diseases associated with bone disorders, such  
as osteoporosis, or associated with excessive secretion of PTH, such as hyperparathy-  
roidism. The subject invention also relates to processes for making such compounds as  
well as to intermediates useful in such processes.

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## CALCIUM RECEPTOR MODULATING AGENTS

This application claims the benefit of U.S. Provisional Application No. 60/441,065, filed January 17, 2003, and U.S. Provisional Application No. 5 60/383,050, filed May 23, 2002, which are hereby incorporated by reference.

**Background of the Invention**

Extracellular calcium ion concentration is involved in a variety of  
10 biological processes, such as blood clotting, nerve and muscle excitability and bone formation (Cell Calcium 11:319, 1990). Calcium ion receptors, which are present on the membranes of various cells in the body, such as parathyroid and kidney cells (Nature 366:574, 1993; J. Bone Miner. Res. 9, Supple. 1, s282, 1994; J. Bone Miner. Res. 9, Supple. 1, s409, 1994; Endocrinology 136:5202, 1995), are  
15 important to the regulation of the extracellular calcium ion concentration. For example, concentration of extracellular calcium ion regulates the bone resorption by osteoclasts (Bioscience Reports 10:493, 1990), secretion of parathyroid hormone (PTH) from parathyroid cells and secretion of calcitonin from C-cells (Cell Calcium 11:323, 1990). Parathyroid hormone (PTH) is an important factor  
20 in regulating extracellular calcium ion concentration. Secretion of PTH increases extracellular calcium ion concentration by acting on various cells, such as bone and kidney cells, and the extracellular calcium ion concentration reciprocally inhibits the secretion of PTH by acting on parathyroid cells.

Several classes of calcimimetic compounds have been disclosed for  
25 regulating extracellular calcium ion concentration, particularly for reducing or inhibiting secretion of PTH. For example, U.S. Patent Nos. 6,011,068 and 5,981,599 disclose arylalkylamines that are calcium receptor active molecules. EP 933354; WO 0021910, WO 96/12697; WO 95/11221; WO 94/18959; WO 93/04373; Endocrinology 128:3047, 1991; Biochem. Biophys. Res. Commun.  
30 167:807, 1990; J. Bone Miner. Res. 5:581, 1990; and Nemeth et al., "Calcium-binding Proteins in Health and Disease," Academix Press, Inc., pp. 33-35 (1987) disclose various agents that interact with calcium receptors.

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Dauban et al., Bioorg. Med. Chem. Let. 10:2001-4, 2000, disclose various N1-arylsulfonyl-N2-(1-aryl)ethyl-3-phenylpropane-1,2-diamine compounds as calcimimetics acting on the calcium sensing receptor.

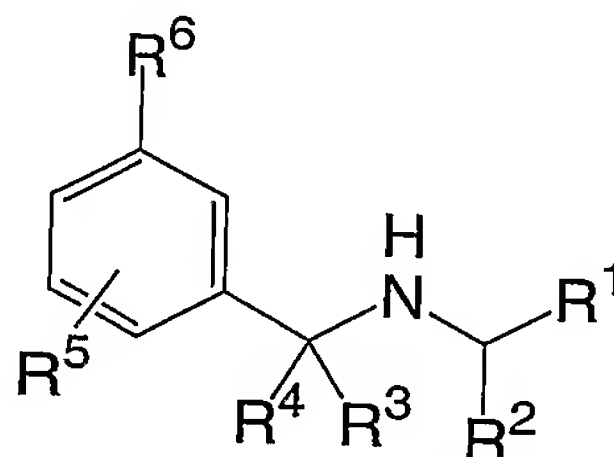
Oikawa et al., in U.S. Patent No. 6,403,832, and publication No. US2002/143212, describes aryl amine compounds useful as chiral intermediates in the synthesis of optically active propionic acid derivatives. Chassot et al., U.S. Patent No. 6,436,152, describes arylalkylamine compounds useful as hair dye precursor compounds.

Bös et al., U.S. Patent No. 6,407,111, describes phenyl substituted pyridine and benzene derivatives that are antagonistic to the NK-1 receptor.

### Summary of the Invention

The present invention relates to selected calcimimetic compounds and pharmaceutically acceptable salts thereof. The invention compounds advantageously reduce or inhibit PTH secretion. Therefore, this invention also encompasses pharmaceutical compositions, methods for reducing or inhibiting PTH secretion and methods for treatment or prophylaxis of diseases associated with bone disorders, such as osteoporosis, or associated with excessive secretion of PTH, such as hyperparathyroidism. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

The compounds of the invention are represented by the following general structure:



or a pharmaceutically acceptable salt thereof, wherein the variables are defined below.

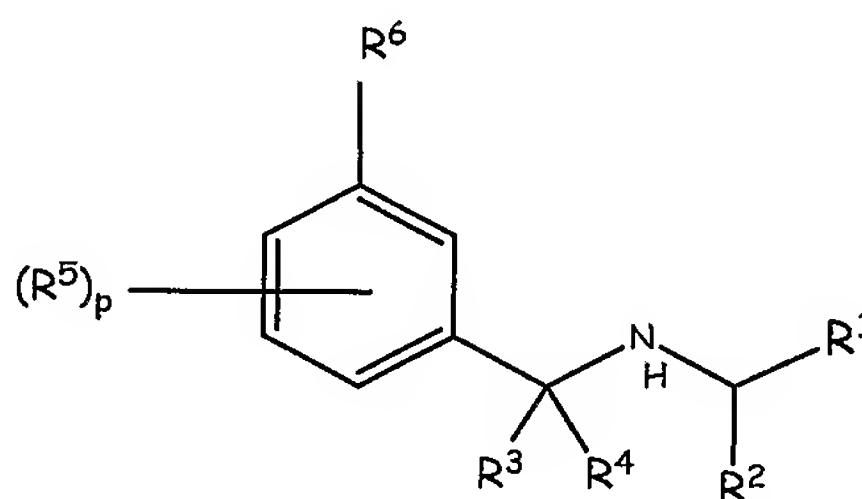
The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All

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patents, patent applications and other publications recited herein are hereby incorporated by reference in their entirety.

### **Detailed Description**

5 The invention provides compounds of Formula (I):



(I)

10 or a pharmaceutically acceptable salt thereof,  
wherein:

$R^1$  is aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, or substituted cycloalkyl;

$R^2$  is alkyl or haloalkyl;

15  $R^3$  is H, alkyl, or haloalkyl;

$R^4$  is H, alkyl, or haloalkyl;

each  $R^5$  present is independently selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, halogen,  $-C(=O)OH$ ,  $-CN$ ,  $-NR^dS(=O)_mR^d$ ,  $-NR^dC(=O)NR^dR^d$ ,  $-NR^dS(=O)_mNR^dR^d$ , or  $-NR^dC(=O)R^d$ ;

20  $R^6$  is aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, or substituted cycloalkyl;

each  $R^a$  is, independently, H, alkyl or haloalkyl;

each  $R^b$  is, independently, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl, each of which may be unsubstituted or substituted by up to 3 substituents selected from the group

25 consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;



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each  $R^c$  is, independently, alkyl, haloalkyl, phenyl or benzyl, each of which may be substituted or unsubstituted;

each  $R^d$  is, independently, H, alkyl, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl wherein the alkyl, aryl, aralkyl, heterocyclyl, and heterocyclylalkyl are substituted by 0, 1, 2, 3 or 4 substituents selected from alkyl, halogen, haloalkyl, alkoxy, cyano, nitro,  $R^b$ ,  $-C(=O)R^c$ ,  $-OR^b$ ,  $-NR^aR^a$ ,  $-NR^aR^b$ ,  $-C(=O)OR^c$ ,  $-C(=O)NR^aR^a$ ,  $-OC(=O)R^c$ ,  $-NR^aC(=O)R^c$ ,  $-NR^aS(=O)_nR^c$  and  $-S(=O)_nNR^aR^a$ ;

m is 1 or 2;

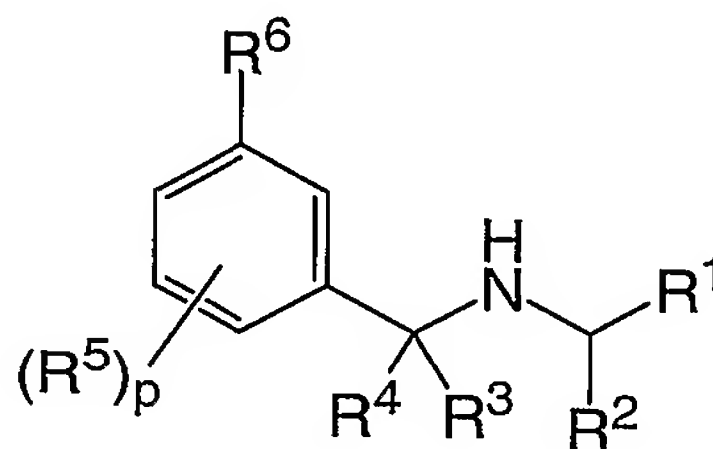
n is 0, 1 or 2; and

p is 0, 1, 2, 3, or 4;

provided that if  $R^2$  is methyl, p is 0, and  $R^6$  is unsubstituted phenyl, then  $R^1$  is not 2,4-dihalophenyl, 2,4-dimethylphenyl, 2,4-diethylphenyl, 2,4,6-trihalophenyl, or 2,3,4-trihalophenyl.

15

Another aspect of the invention relates to compounds having the general structure II:



20

(II)

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$  is phenyl, benzyl, naphthyl or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl or heterocycle are substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro;

25

$R^2$  is  $C_{1-8}$ alkyl or  $C_{1-4}$ haloalkyl;

$R^3$  is H,  $C_{1-4}$ haloalkyl or  $C_{1-8}$ alkyl;

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$R^4$  is H,  $C_{1-4}$ haloalkyl or  $C_{1-8}$ alkyl;

$R^5$  is, independently, in each instance, H,  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halogen, cyano,  $-NR^aR^d$ ,  $-NS(=O)_2R^c$ ,  $-NR^aC(=O)NR^aR^d$ ,  $-NR^dC(=O)R^d$  or  $-OC_{1-6}$ alkyl substituted by 0, 1, 2 or 3 substituents selected from halogen,  $-OC_{1-6}$ alkyl,  $-NR^aR^d$ ,  
 5  $-NS(=O)_2R^c$ ,  $-NR^aC(=O)NR^aR^d$ ,  $-NR^dC(=O)R^d$  or cyano;

$R^6$  is phenyl, benzyl, naphthyl, a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, or a saturated or unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4 or 5  
 10 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl, naphthyl, heterocycle and heterobicycle are substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro;

15  $R^a$  is, independently, at each instance, H,  $C_{1-4}$ haloalkyl or  $C_{1-6}$ alkyl;

$R^b$  is, independently, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl, each of which may be unsubstituted or substituted by up to 3 substituents selected from the group consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

20  $R^c$  is, independently, at each instance,  $C_{1-6}$ alkyl,  $C_{1-4}$ haloalkyl, phenyl or benzyl;

$R^d$  is, independently, at each instance, H,  $C_{1-6}$ alkyl, phenyl, benzyl or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the  $C_{1-6}$ alkyl, phenyl, benzyl, naphthyl and heterocycle are  
 25 substituted by 0, 1, 2, 3 or 4 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro,  $R^b$ ,  $-C(=O)R^c$ ,  $-OR^b$ ,  $-NR^aR^a$ ,  $-NR^aR^b$ ,  $-C(=O)OR^c$ ,  $-C(=O)NR^aR^a$ ,  $-OC(=O)R^c$ ,  $-NR^aC(=O)R^c$ ,  $-NR^aS(=O)_mR^c$  and  $-S(=O)_mNR^aR^a$ ;

$m$  is 1 or 2;

30  $n$  is 0, 1 or 2; and

$p$  is 0, 1, 2, 3 or 4.

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In one embodiment, in conjunction with any one of the above and below embodiments,  $R^1$  is phenyl substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.

5 In another embodiment, in conjunction with any one of the above and below embodiments,  $R^1$  is benzyl substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments,  $R^1$  is naphthyl substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.

10 In another embodiment, in conjunction with any one of the above and below embodiments,  $R^1$  a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  
15  $-OC_{1-6}$ alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments,  $R^6$  is phenyl, wherein the phenyl is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.

20 In another embodiment, in conjunction with any one of the above and below embodiments,  $R^6$  is benzyl, wherein the benzyl is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments,  $R^6$  is naphthyl, wherein the naphthyl is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments,  $R^6$  is a saturated or unsaturated 5- or 6-membered ring  
30 heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,

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-OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>6</sup> is a saturated or unsaturated 8-, 9-, 10- or 11-membered  
5 heterobicycle containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterobicycle is substituted by 0, 1, 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.

10 In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>1</sup> is phenyl, naphthyl or (OC<sub>1-4</sub>alkyl)phenyl.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>1</sup> is phenyl substituted by 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, cyano and nitro.

15 In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>1</sup> is benzyl substituted by 1, 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>1</sup> is naphthyl substituted by 1, 2 or 3 substituents selected  
20 from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>1</sup> is a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted  
25 by 1, 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, one of R<sup>3</sup> or R<sup>4</sup> is C<sub>1-4</sub>haloalkyl or C<sub>1-8</sub>alkyl.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>5</sup> is C<sub>1-8</sub>alkyl, C<sub>1-4</sub>haloalkyl, halogen or -OC<sub>1-6</sub>alkyl.  
30

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>6</sup> is phenyl, wherein the phenyl is substituted by 1, 2 or 3

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substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>6</sup> is benzyl, wherein the benzyl is substituted by 1, 2 or 3  
5 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>6</sup> is naphthyl, wherein the naphthyl is substituted by 0, 1, 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl,  
10 -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>6</sup> is a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted  
15 by 1, 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R<sup>6</sup> is a saturated or unsaturated 8-, 9-, 10- or 11-membered  
20 heterobicycle containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterobicycle is substituted by 1, 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.

25 Another aspect of the invention involves a pharmaceutical composition comprising a pharmaceutically acceptable amount of a compound according to any one of the above embodiments and a pharmaceutically acceptable diluent or carrier.

Another aspect of the inventions involve the use of a compound according  
30 to any one of the above embodiments as a medicament.

Another aspect of the invention involves the use of a compound according to any one of the above embodiments in the manufacture of a medicament for the



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treatment of diseases associated with bone disorders or associated with excessive secretion of PTH.

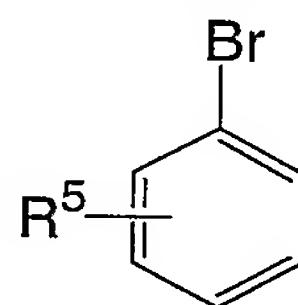
Another aspect of the invention involves the use of a compound according to any one of the above embodiments in the manufacture of a medicament for the treatment of osteoporosis or hyperparathyroidism.

Another aspect of the invention involves a method of using a compound according to any one of the above embodiments for the treatment of diseases associated with bone disorders or associated with excessive secretion of PTH.

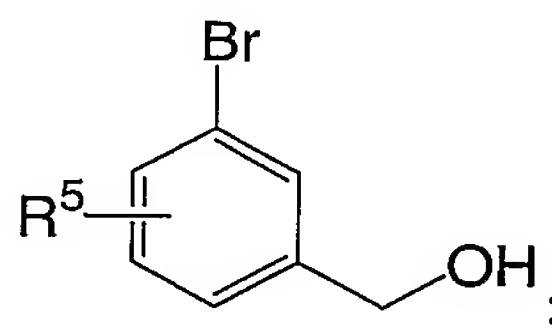
Another aspect of the invention involves a method of using a compound according to any one of the above embodiments for the treatment of osteoporosis or hyperparathyroidism.

Another aspect of the invention involves a process for making a compound according to Claim 1 wherein  $R^3$  and  $R^4$  are both hydrogen comprising the steps of:

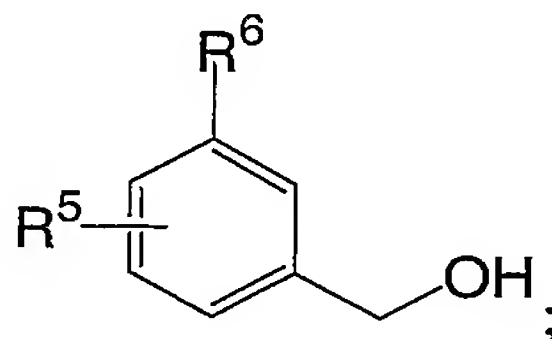
placing a compound having the structure



in the presence of acid followed by treatment with a hydride and methanol to form

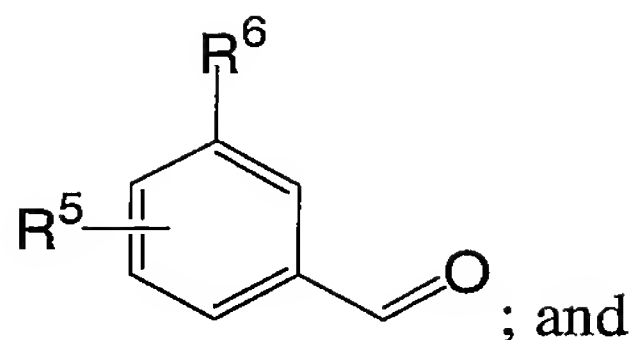


reacting the resulting alcohol with  $R^6$ -B(OH)<sub>2</sub> to form

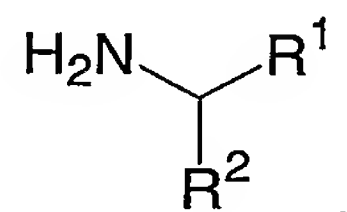


oxidizing the alcohol to form

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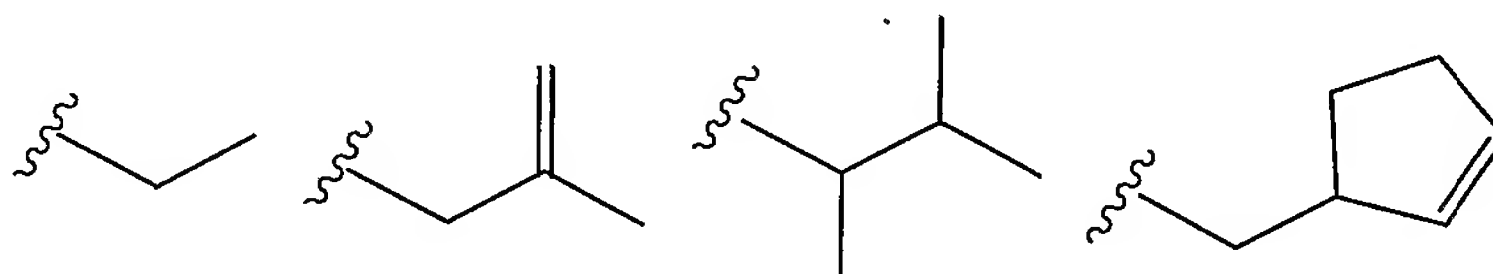


reacting the aldehyde with an amine having the structure



Unless otherwise specified, the following definitions apply to terms found  
5 in the specification and claims:

“Alkyl” and the prefix “alk-” refer to alkyl groups or substituents wherein  
the carbon atoms are in a branched, cyclical or linear relationship or any  
combination of the three. The alkyl groups described in this section contain from  
1 to 10 carbon atoms unless otherwise specified and may also contain a double or  
10 triple bond. “C<sub>V-W</sub>alkyl” means an alkyl group comprising from V to W carbon  
atoms. Examples of C<sub>1-6</sub>alkyl include, but are not limited to the following:



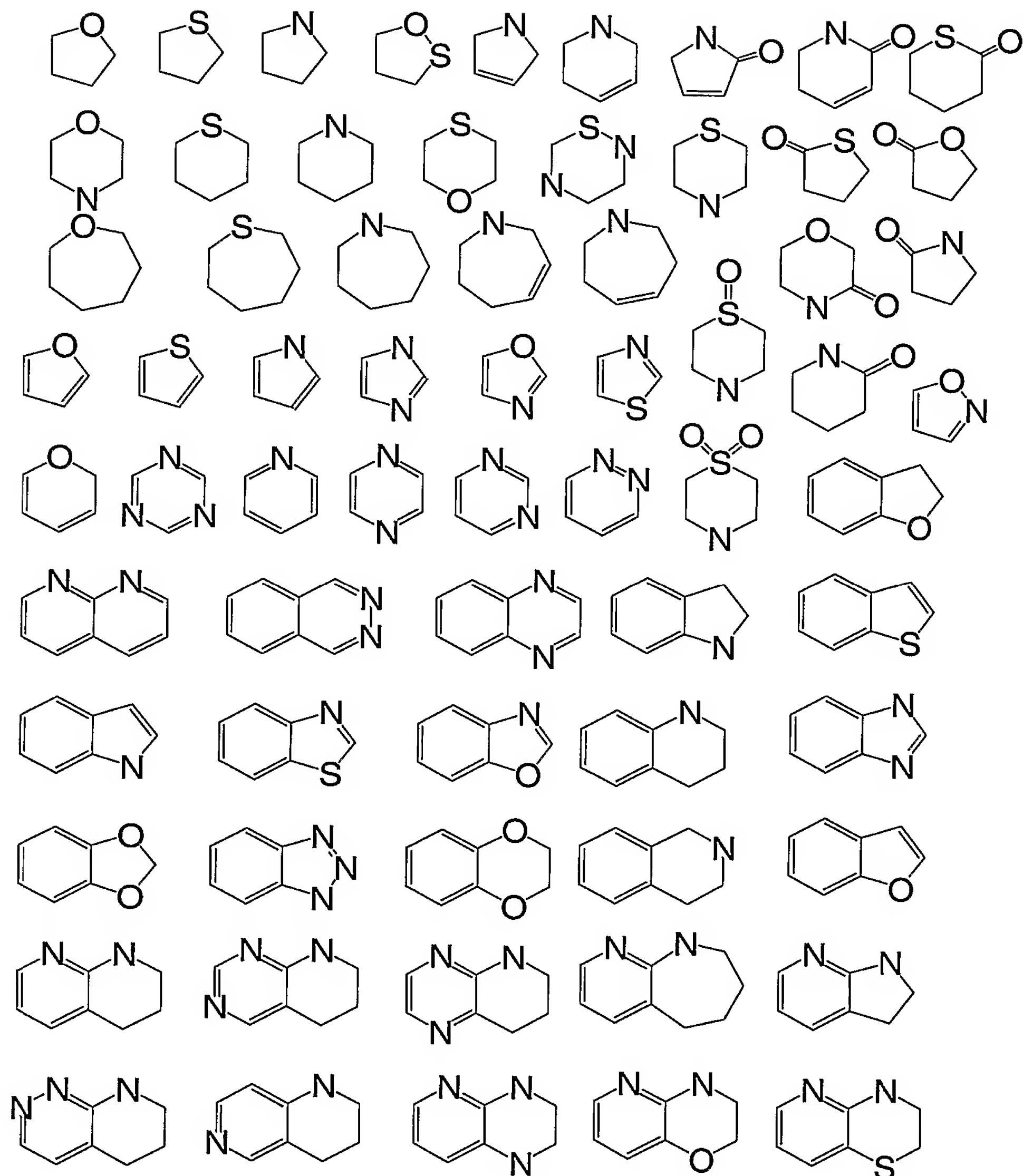
“Aryl” means a carbocyclic aromatic ring or ring system. Examples of  
aryl groups include phenyl, naphthyl, indenyl, fluorenyl, biphenyl, anthracenyl, 9-  
15 (9-phenylfluorenyl), phenanthrenyl, and the like.

“Halogen” means a halogen atom selected from F, Cl, Br and I.

“Haloalkyl”, “haloalk-” and “C<sub>V-W</sub>haloalkyl” mean an alkyl group, as  
described above, wherein any number--at least one--of the hydrogen atoms  
attached to the alkyl group or chain are replaced by F, Cl, Br or I.

20 “Heterocycle” means a ring or ring system comprising at least one carbon  
atom and at least one other atom selected from N, O and S. Heterocyclic groups  
can be saturated, unsaturated or aromatic. Aromatic heterocyclic groups are also  
referred to as “heteroaryl” rings or ring systems. Examples of heterocycles that  
may be found in the claims include, but are not limited to, the following:

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Unless otherwise specified, the term “substituted” means that a group is substituted by one or more substituents independently selected from the group consisting of hydroxy, alkyl, alkoxy, alkylthio, halogen, haloalkyl, haloalkoxy, alkylcarbonyl, haloalkylcarbonyl, arylcarbonyl, heterocyclcarbonyl, aryl, aralkyl, heterocycl, heterocyclalkyl, -CN, -C(=O)OH, alkoxycarbonyl, alkanoyloxy, alkanoylthio, nitro, -N(R<sup>a</sup>)<sub>2</sub>, -N(R<sup>a</sup>)(R<sup>b</sup>), NR<sup>d</sup>S(=O)<sub>2</sub>R<sup>d</sup>, -NR<sup>d</sup>C(=O)NR<sup>d</sup>R<sup>d</sup>, -NR<sup>d</sup>S(=O)<sub>2</sub>NR<sup>d</sup>R<sup>d</sup>, or -NR<sup>d</sup>C(=O)R<sup>d</sup> and, in the case of heterocycl cycloalkyl groups, oxo.

10

Preferred compounds include:

- (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 10 (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine;
- 20 (1R)-N-((3-(1-methyl-1H-benzimidazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 30 (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 35 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 40 ethyl 4-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3,6-dihydro-1(2H)-pyridinecarboxylate;
- (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 45 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
5 (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
10 (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
15 (1R)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
20 (1R)-N-((4-chloro-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridiny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
25 (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
30 (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-fluorophenyl)ethanamine;  
35 (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
40 (1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;  
45 1-(3-bromophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;  
1-(3,5-difluorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;



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- (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 10 (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((6-iodo-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-iodo-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 15 (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 ethyl 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- ethyl 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- 25 4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1,3-thiazol-2-amine;
- (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 30 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 35 (1R)-N-((3-(2-fluoro-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- N,N-dimethyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 40 (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 45 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)ethanamine;

- (1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 10 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 15 (1R)-N-((6-(ethyloxy)-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine
- 25 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine;
- 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- 30 (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 35 (1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-(4-morpholinyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 40 (1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-phenylethanamine;
- 45 ethyl 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-methylphenyl)ethanamine;

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- (1R)-N-((6-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;  
5 N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;  
N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;  
(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
10 (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;  
15 (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(6-quinolalanyl)phenyl)methyl)-1-phenylethanamine;  
20 (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
25 (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-phenylethanamine;  
30 (1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
(1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-phenylethanamine;  
35 (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinolalanyl)phenyl)methyl)ethanamine;  
40 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;  
(1R)-1-(1-naphthalenyl)-N-((3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;  
45 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;

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(1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
 (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 5 (1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 10 (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
 (1R)-N-((3-(2-ethyl-2H-1,2,3-benzotriazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine; and  
 (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

15 Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional
 20 processes, *e.g.*, by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for
 25 separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be
 30 separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt. The (R) isomer is generally preferred.

35 Likewise, the compounds of this invention may exist as isomers, that is compounds of the same molecular formula but in which the atoms, relative to one another, are arranged differently. In particular, the alkylene substituents of the



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compounds of this invention, are normally and preferably arranged and inserted into the molecules as indicated in the definitions for each of these groups, being read from left to right. However, in certain cases, one skilled in the art will appreciate that it is possible to prepare compounds of this invention in which these substituents  
5 are reversed in orientation relative to the other atoms in the molecule. That is, the substituent to be inserted may be the same as that noted above except that it is inserted into the molecule in the reverse orientation. One skilled in the art will appreciate that these isomeric forms of the compounds of this invention are to be construed as encompassed within the scope of the present invention.

10 The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate,  
15 ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, mandelate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 2-phenylpropionate, picrate, pivalate, propionate, salicylate, succinate, sulfate,  
20 tartrate, thiocyanate, tosylate, mesylate, and undecanoate. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in  
25 the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," *see infra* and Berge et al., J. Pharm. Sci. 66:1 (1977).

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and  
30 iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and



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iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Also encompassed in the scope of the present invention are pharmaceutically acceptable esters of a carboxylic acid or hydroxyl containing group, including a metabolically labile ester or a prodrug form of a compound of this invention. A metabolically labile ester is one which may produce, for example, an increase in blood levels and prolong the efficacy of the corresponding non-esterified form of the compound. A prodrug form is one which is not in an active form of the molecule as administered but which becomes therapeutically active after some in vivo activity or biotransformation, such as metabolism, for example, enzymatic or hydrolytic cleavage. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bundgaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use. Esters of a compound of this invention, may include, for example, the methyl, ethyl, propyl, and butyl esters, as well as other suitable esters formed between an acidic moiety and a hydroxyl containing moiety. Metabolically labile esters, may include, for example, methoxymethyl, ethoxymethyl, iso-propoxymethyl,  $\alpha$ -methoxyethyl, groups such as  $\alpha$ -((C<sub>1</sub>-C<sub>4</sub>)alkyloxy)ethyl; for example, methoxyethyl, ethoxyethyl, propoxyethyl, iso-propoxyethyl, etc.; 2-oxo-1,3-dioxolen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, etc.; C<sub>1</sub>-C<sub>3</sub> alkylthiomethyl groups, for example, methylthiomethyl, ethylthiomethyl, isopropylthiomethyl, etc.; acyloxymethyl

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groups, for example, pivaloyloxymethyl,  $\alpha$ -acetoxymethyl, etc.; ethoxycarbonyl-1-methyl; or  $\alpha$ -acyloxy- $\alpha$ -substituted methyl groups, for example  $\alpha$ -acetoxymethyl.

Further, the compounds of the invention may exist as crystalline solids which can be crystallized from common solvents such as ethanol, N,N-dimethyl-  
5 formamide, water, or the like. Thus, crystalline forms of the compounds of the invention may exist as solvates and/or hydrates of the parent compounds or their pharmaceutically acceptable salts. All of such forms likewise are to be construed as falling within the scope of the invention.

"Leaving group" generally refers to groups readily displaceable by a  
10 nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

15 "Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include,  
20 but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl alkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such  
25 as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkenylalkyl radicals, preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxycarbonyl and aralkoxycarbonyl groups  
30 include benzyloxycarbonyl, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino

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group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxycarbonyl group. Amino protecting groups can also form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and  
5 where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many of the  
10 amino protecting groups are also suitable for protecting carboxy, hydroxy and mercapto groups. For example, aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-butyl.

Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but  
15 are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyl dimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of an amino groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-tri-silyl derivative. Removal of the silyl function  
20 from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyl dimethylsilyl chloride, diphenylmethyl silyl chloride or their combination  
25 products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol  
30 chemistry.

Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and

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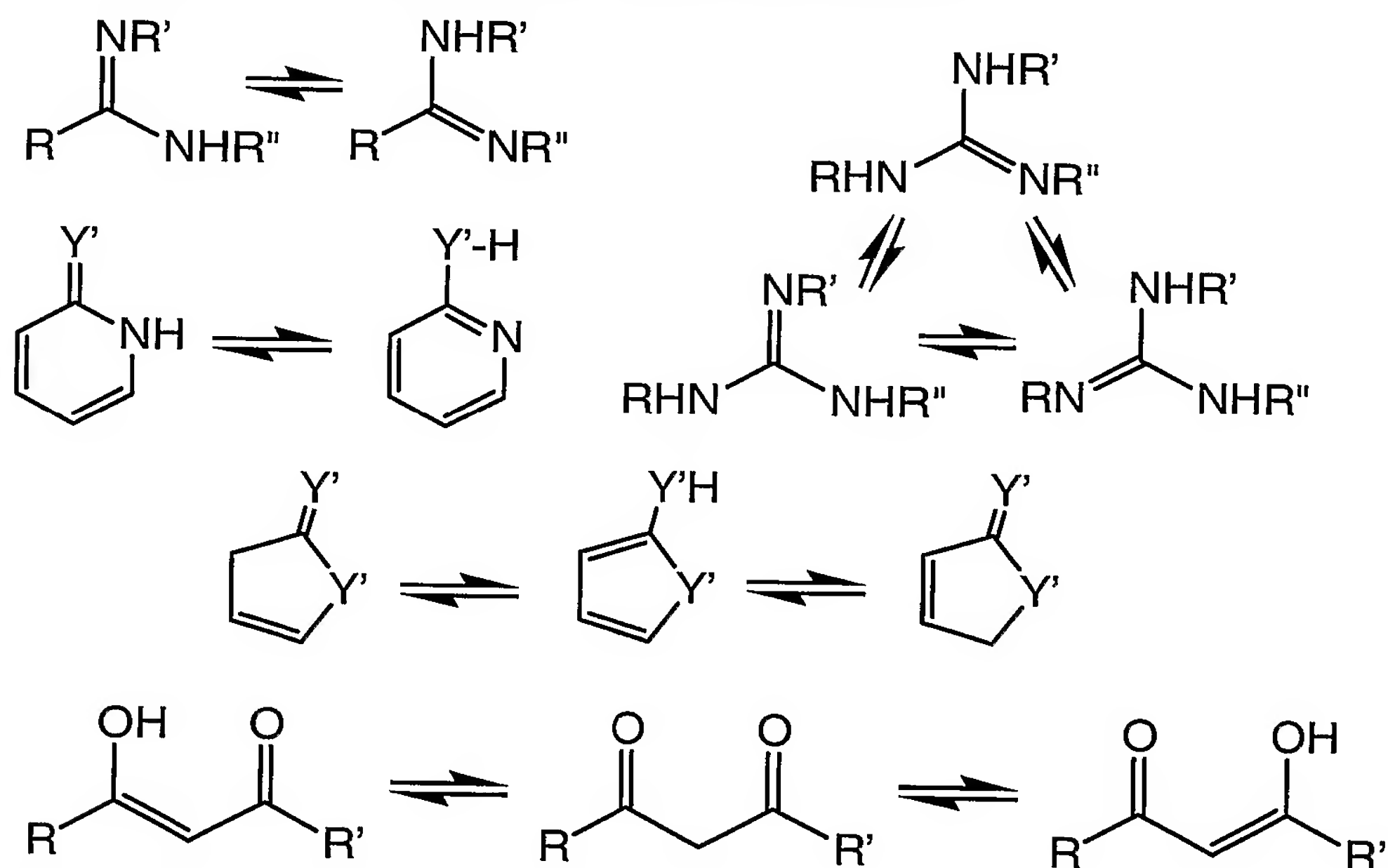
include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzyloxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-

5 butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can readily be neutralized to yield the free amine. Carboxy protecting group, such as methyl, ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed

10 under hydrolysis and hydrogenolysis conditions well known to those skilled in the art.

It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as cyclic and acyclic amidine and guanidine groups, heteroatom substituted heteroaryl groups ( $Y' = O, S, NR$ ), and

15 the like, which are illustrated in the following examples:



and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

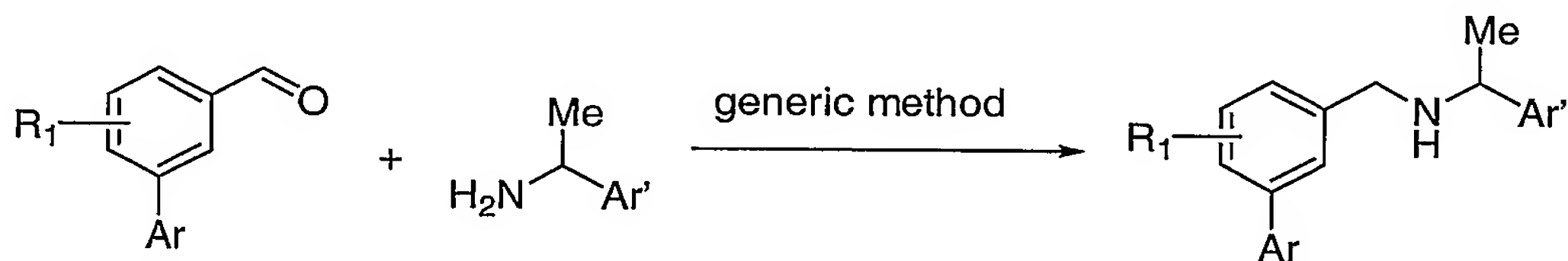
20 A "derivative" of a compound of the invention includes salts, isomers, enantiomers, prodrugs, and metabolites of the compound.

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Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek, Drug Metabolism Reviews 165 (1988) and Bundgaard, Design of Prodrugs, Elsevier (1985). One method of preparing a prodrug of a compound is by masking one or more potentially reactive groups on the compound, such as carboxylates, hydroxy groups, and amines. Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bungaard, J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

### Experimental

General:



**Method A:** the aldehyde (1.6 mmol) is dissolved in methanol (5 mL) and the amine (1.9 mmol) is added. The reaction is shaken for 24 hours or until imine formation is complete (as monitored by LCMS), then solid supported borohydride is added (prepared according to Kabalka, G. W.; Wadgaonkar, P. P.; Chatla, N.; *Synth. Commun.*; (1990), 20 (2), 293-299) (ca 2.5mmol/g; 3.1 mmol) and the



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mixture is shaken for 24 hours or until reduction is complete (as monitored by LCMS). Dichloromethane (*ca* 3 mL) is then added followed by Wang-aldehyde resin (4-benzyloxybenzaldehyde, polymer-bound; *ca* 1.25mmol/g; 0.6mmol) and the mixture is shaken for further 24 hours. The resins are filtered off and the solvents are evaporated under reduced pressure, to afford an oil which is purified by column chromatography (usually Hexane/AcOEt 7/3 or DCM/MeOH 95/5). The free-base oil is then treated with 1.5-2.5 1N HCl in diethyl ether and the solvents are evaporated under reduced pressure to afford the *mono* or *bis*-HCl salt.

**Method B:** the aldehyde (1.6 mmol) is dissolved in methanol (5 mL) and the amine (1.9 mmol) is added. The reaction is heated to reflux for 10 minutes then left to cool overnight until imine formation is complete (as monitored by LCMS). Solid supported cyanoborohydride is added (prepared according to Sande, A. R.; Jagadale, M. H.; Mane, R. B.; Salunkhe, M. M.; *Tetrahedron Lett.* (1984), 25(32), 3501-4) (*ca* 2.5 mmol/g; 3.1 mmol) and the mixture is heated at 50 C for 15 hours or until reduction is complete (as monitored by LCMS). Dichloromethane (*ca* 3 mL) is then added followed by Wang-aldehyde resin (4-benzyloxybenzaldehyde, polymer-bound; *ca* 1.25 mmol/g; 0.6 mmol) and the mixture is shaken for further 24 hours. The resins are filtered off and the solvents are evaporated under reduced pressure, to afford an oil which is purified by column chromatography (usually Hexane/AcOEt 7/3 or DCM/MeOH 95/5). The free-base oil is then treated with 1.5-2.5 1N HCl in diethyl ether and the solvents are evaporated under reduced pressure to afford the *mono* or *bis*-HCl salt.

**Method C:** The aldehyde (1.6 mmol) is dissolved in 1,2-dichloroethane (12 mL) and the amine (1.9 mmol) is added, followed by acetic acid (0.09 mL, 1.6 mmol) and finally sodium triacetoxyborohydride (500 mg, 2.4 mmol). The mixture is stirred overnight or until complete by TLC; upon reaction completion, the mixture is diluted with ethyl acetate, washed with saturated NaHCO<sub>3</sub> then with saturated brine, and finally dried over sodium sulphate. The solvents are evaporated under reduced pressure, to afford an oil which is purified by column chromatography on silica gel (usually Hexane/AcOEt 7/3 or DCM/MeOH 95/5). The free-base oil is then treated with 1.5-2.5 equivalents 1N HCl in diethyl ether

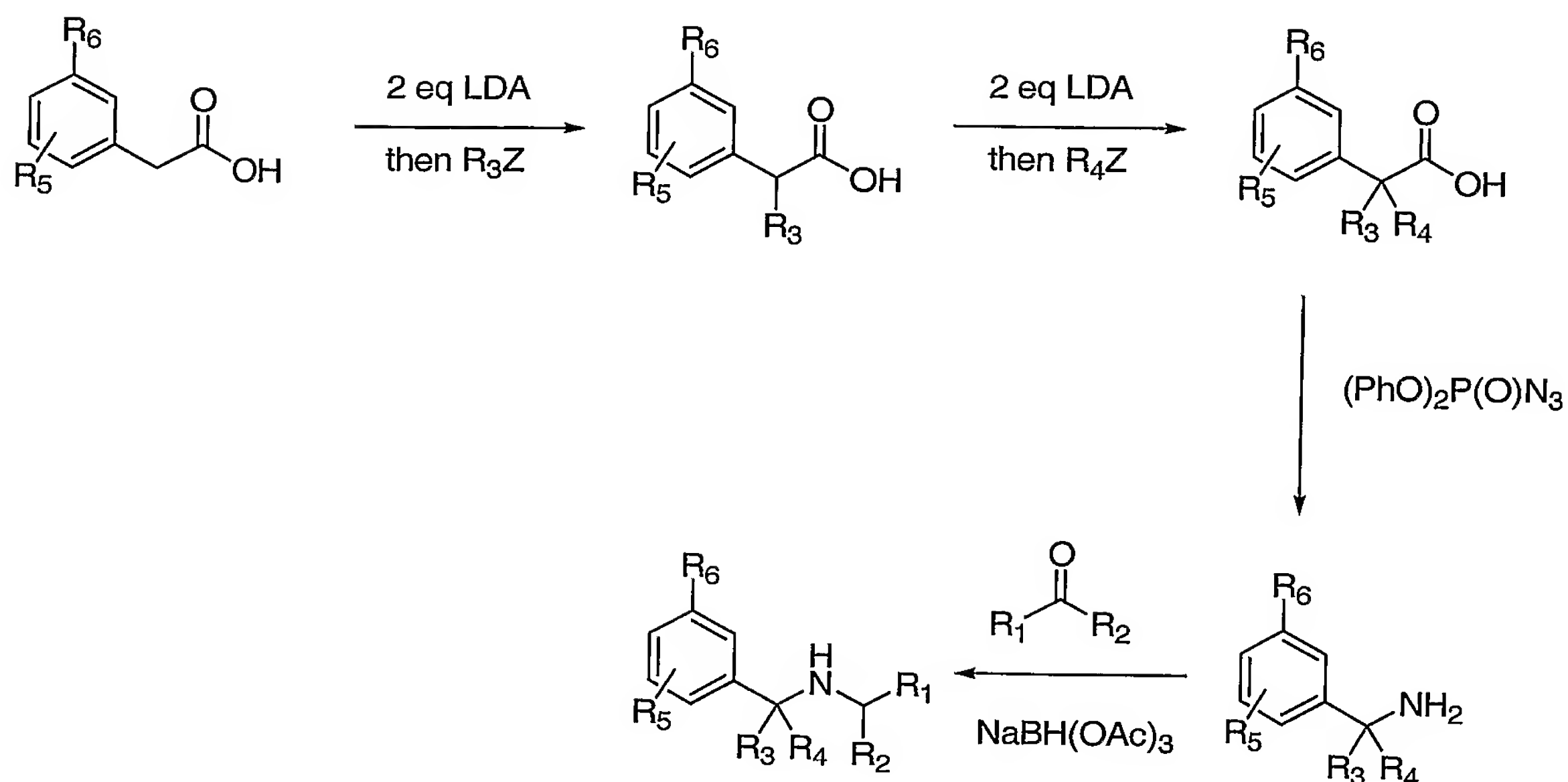
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and the solvents are evaporated under reduced pressure to afford the *mono* or *bis*-HCl salt.

**Method D:** Compounds wherein both  $R^3$  and  $R^4$  are other than hydrogen can be prepared by combining an appropriately substituted phenylacetic acid with a strong base such as lithium diisopropylamide or the like at a temperature between  $-78$  and  $20^\circ\text{C}$  to yield a red dianion. The dianion is then reacted with an alkylating agent of formula  $R^3\text{-Z}$ , wherein Z is a halide, a sulfonate, or other suitable leaving group to provide an  $R^3$  substituted compound. Treatment of the compound thus obtained with a strong base such as lithium diisopropylamide or the like at a temperature between  $-78$  and  $20^\circ\text{C}$  yields a second red dianion, which is reacted with an alkylating agent of formula  $R^4\text{-Z}$ , wherein Z is a halide, a sulfonate, or other suitable leaving group to yield the  $R^3, R^4$  disubstituted compound. Treatment of the resultant carboxylic acid with diphenylphosphoryl azide in a refluxing solvent (for example toluene, benzene, chlorobenzene, 1,4-dioxane or the like), followed by aqueous workup yields the  $R^3$  substituted  $R^4$  amine. Reductive coupling of the amine with an aldehyde or ketone according to Method C affords the final product.

**Method E:** Compounds wherein only one of  $R^3$  and  $R^4$  is hydrogen can be prepared by reacting the  $\alpha$ -monosubstituted carboxylic acid obtained by reacting an appropriately substituted phenylacetic acid with a strong base such as lithium diisopropylamide and then with an alkylating agent of formula  $R^3\text{-Z}$  as described above with diphenylphosphoryl azide in a refluxing solvent such as, for example, toluene, benzene, chlorobenzene, 1, 4-dioxane, etc. followed by an aqueous workup to yield a mono- $\alpha$ -substituted amine. This amine can then be reacted with an aldehyde or ketone according to Method C to obtain the final product.

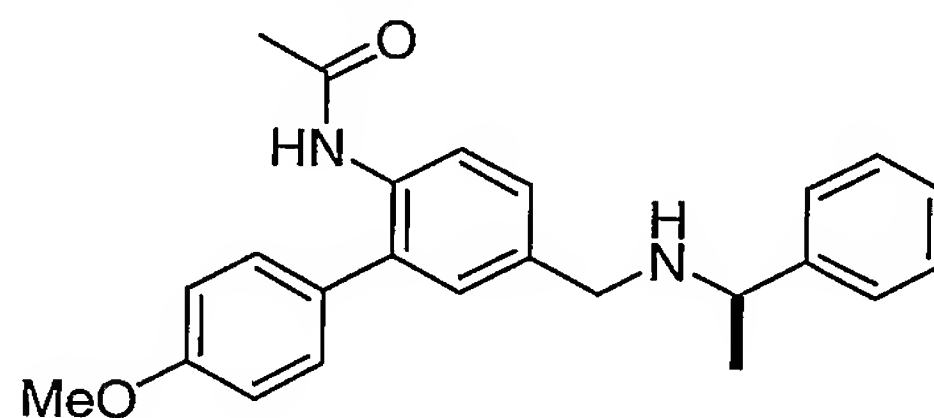
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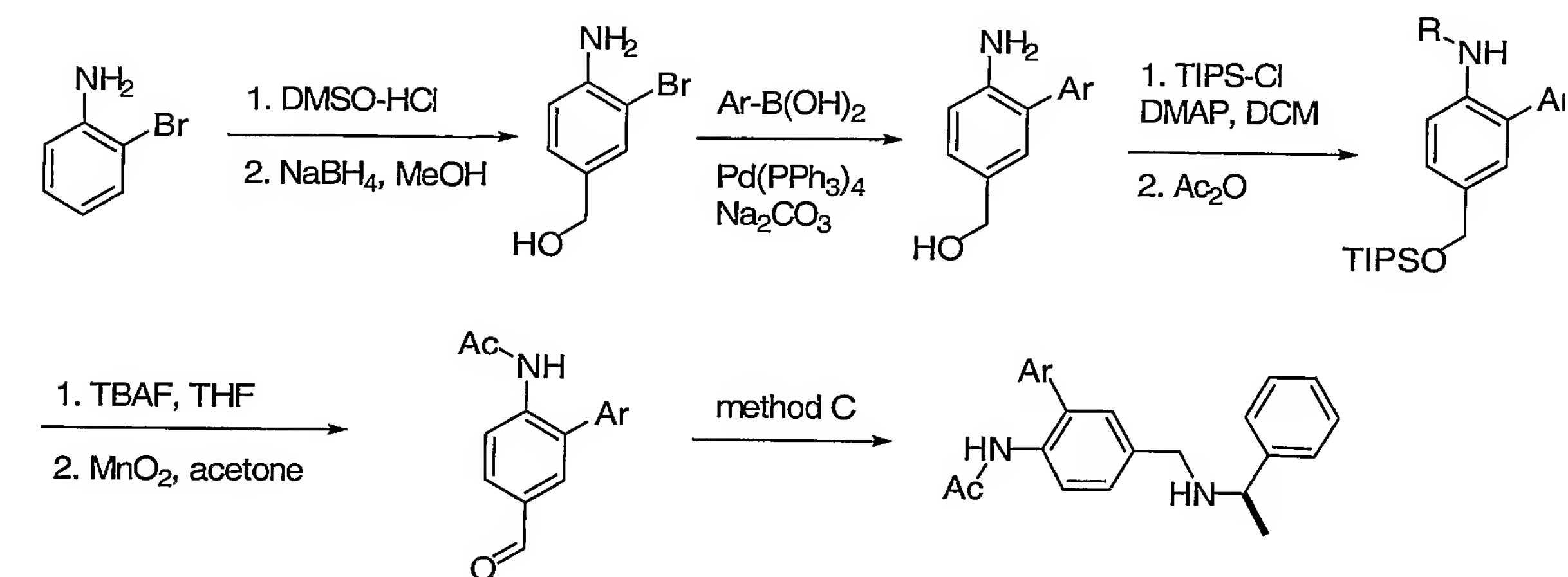
The following examples are representative of the invention, but are not to  
 be construed as limiting the claimed invention in any way. The structure of the  
 prepared compounds is verified by mass spectral data;  $C^{13}$  NMR data is also  
 provided for some compounds. For some compounds, ions having mass greater  
 than  $M+H$  are reported. These ions generally represent dimers or trimers of the  
 synthesized compound, and in some instances represent trifluoroacetate adducts  
 generated from the mobile phase of the LC/MS. The trifluoroacetate adducts will  
 have a weight of  $M+115$ .

### Example 1

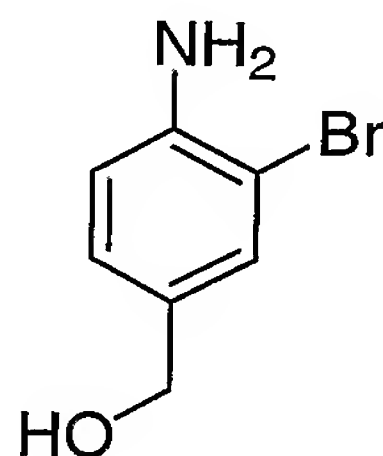
(R)-N-(1-phenylethyl)-N-((4-acetamido-3-(4-methoxyphenyl)phenyl)methyl)amine



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Step1) 2-bromo-4-hydroxymethylaniline:

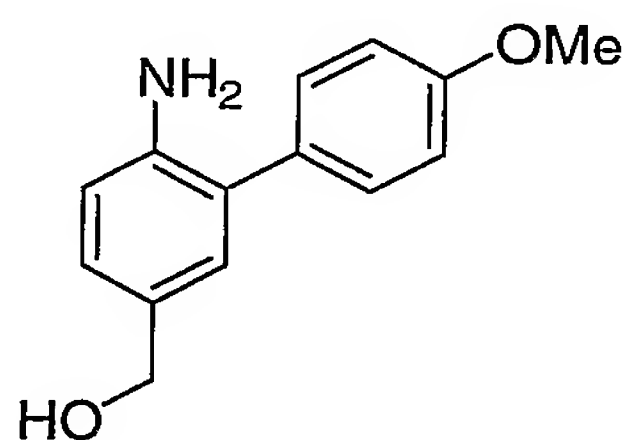


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To a solution of 4-amino-3-bromobenzaldehyde (2.6 g, 13 mmol) (prepared as in *J. Chem. Soc., Perkin Trans. 1* (1992), 2235) in methanol (130 mL) solid supported borohydride 6.2 g, 15.5 mmol) was added. The reaction was stirred for 1.5 hours at room temperature, then the resin filtered off and rinsed with little methanol. The filtrate was concentrated in vacuo to give 2.58 g of a brown oil. C<sub>7</sub>H<sub>8</sub>BrNO Mass (calculated) [202.05]; (found) [M<sup>+</sup>] = 202 (bromine); Lc Rt = 0.63, 89%.

Step 2) 4-Hydroxymethyl-2-(4'-methoxyphenyl)aniline:

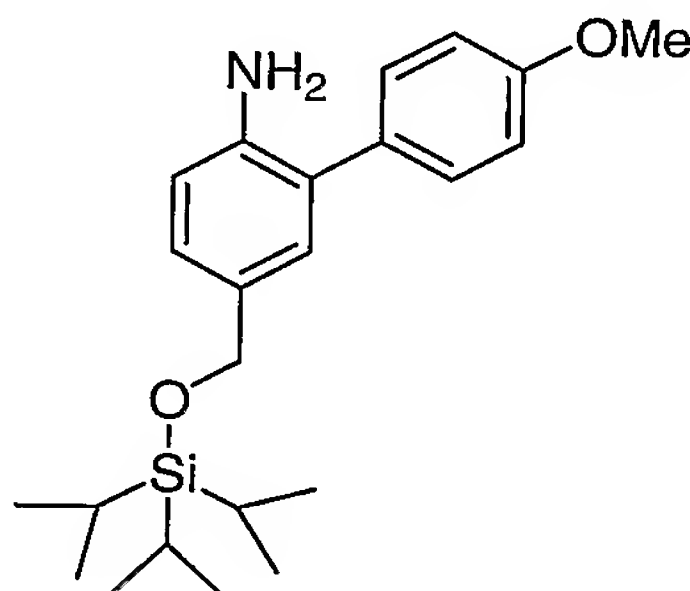
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To a degassed solution of crude 2-bromo-4-hydroxymethylaniline (3.2 g, 15.8 mmol), 4-methoxybenzeneboronic acid (2.89 g, 19 mmol) and potassium carbonate (4.77 g, 34.8 mmol) in toluene/ethanol 2/1 (45 mL) a catalytic amount of  $\text{Pd}(\text{PPh}_3)_4$  (0.2 g, 1mmol%) was added and the mixture was heated at 90 C for 5 hours. The residue was extracted into ethyl acetate and washed with water and then saturated brine and dried over sodium sulphate. The solvent was removed under reduced pressure to afford 5 g of crude product.  $\text{C}_{14}\text{H}_{15}\text{BNO}_2$  Mass (calculated) [229.28]; (found)  $[\text{M}+\text{H}^+] = 230$  Lc Rt = 0.88, 89%. NMR (400 MHz,  $\text{CDCl}_3$ ): 3.75 (3H, s, MeO); 4.5 (2H, s,  $\text{CH}_2\text{O}$ ); 6.65 (1H, d,  $J = 8.5$  Hz, aryl-H); 6.9 (2H, d,  $J = 8.5$  Hz, aryl-H); 7-7.1 (2H, m, aryl-H); 7.25 (2H, d,  $J = 8.5$  Hz, aryl-H).

Step 3) 4-Tri-isopropoxymethyl-2-(4'-methoxyphenyl)aniline:



15

To a solution of the crude alcohol from Step2 and 4-dimethylaminopyridine (2.12 g, 17.4 mmol) in dichloromethane (45 mL) tri-isopropylsilyl chloride (3.05 g, 15.8 mmol) was added. The reaction was stirred at room temperature for 16 hours and then diluted with dichloromethane and washed with water. The organic phase was dried over sodium sulphate and the solvent removed in vacuo. The crude was purified by column (silica, 5%-10 AcOEt in hexane to 10% methanol in AcOEt) to give 4.70 g of title compound.

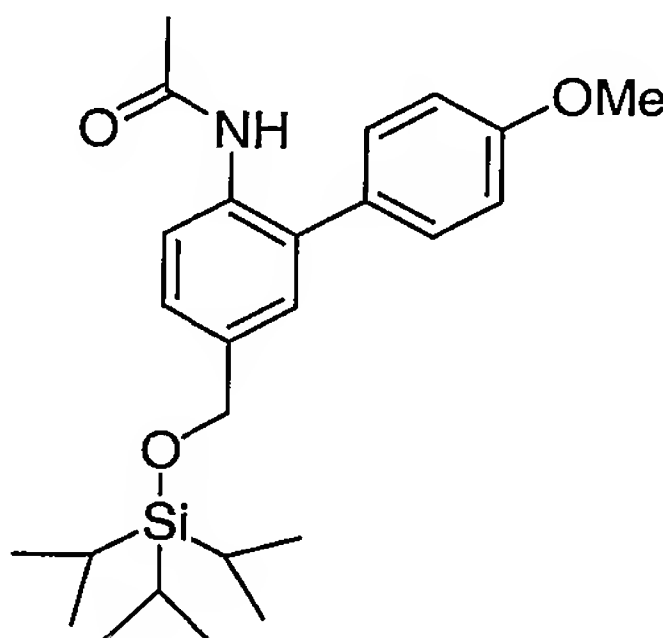
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$\text{C}_{23}\text{H}_{35}\text{NO}_2\text{Si}$  Mass (calculated) [385.63]; (found)  $[\text{M}+\text{H}^+] = 386$  Lc Rt = 1.77.

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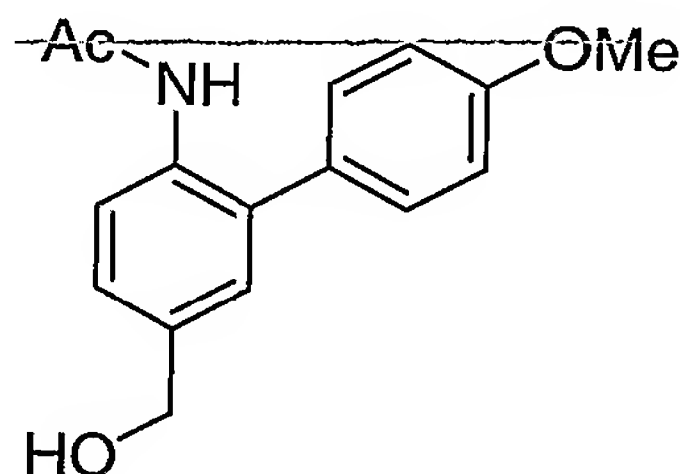


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Step 4) 4-Tri-*isopropoxymethyl*-2-(4'-methoxyphenyl)acetanilide:

To a solution of 4-tri-*isopropoxymethyl*-2-(4'-methoxyphenyl)aniline (1.57 g, 4.07 mmol) and 4-pyridine (0.35 mg, 4.48 mmol) in dichloromethane (9 mL), acetic anhydride (0.4 mL, 4.27 mmol) was added and the reaction stirred at room temperature for 72 hours. The reaction mixture was then diluted with dichloromethane and washed with saturated ammonium chloride and water, then dried over sodium sulphate to afford 1.87 g of a solid.

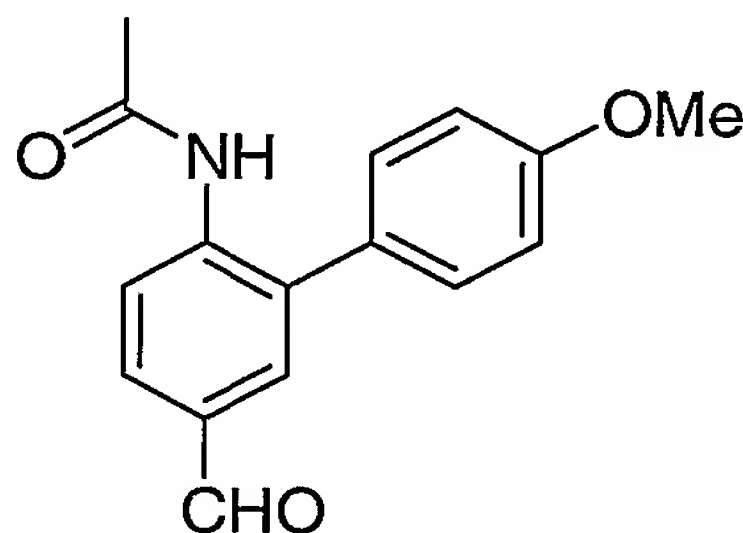
$C_{25}H_{37}NO_3Si$  Mass (calculated) [427.66]; (found)  $[M+H^+] = 428$ ; Lc Rt = 2.10.

Step 5) 4-Hydroxymethyl-2-(4'-methoxyphenyl)acetanilide:

*Tetra*-butylammonium fluoride (4.48 mL of a 1M solution in THF) was added to a solution of 4-tri-*isopropoxymethyl*-2-(4'-methoxyphenyl)acetanilide (1.87 g, 4.07 mmol) in THF (12 mL) and stirred for 2 hours. The reaction was diluted with ethyl acetate and washed with saturated ammonium chloride then water and finally dried over sodium sulphate. The solvent was evaporated to afford 1.66 g of a yellow oil.

$C_{16}H_{17}NO_3$  Mass (calculated) [271.32]; (found)  $[M+H^+] = 272$ ; Lc Rt = 0.95.

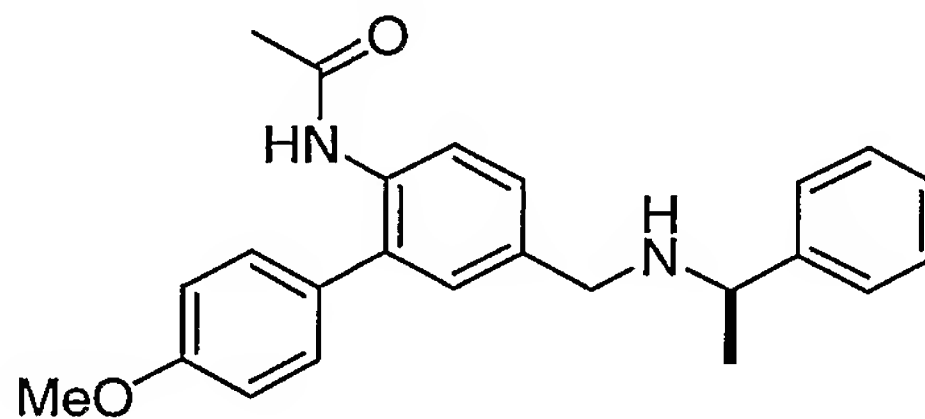
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Step 6) 4-Acetamido-3-(4'-methoxyphenyl)benzaldehyde:

Manganese dioxide (1.77 g, 20.3 mmol) was added portionwise to a stirred  
 5 solution of the crude alcohol (1.66 g) from step 5 in acetone (12 mL). The reaction  
 was stirred at room temperature for 20 hours, then refluxed for a further 8 hours.  
 The reaction mixture was then filtered on paper and the solvent removed under  
 reduced pressure. The crude was purified on silica (hexane/AcOEt 3/1) to give 0.6  
 g of title product.

10  $C_{16}H_{15}NO_3$  Mass (calculated) [269.30]; (found)  $[M+H^+] = 270$ ; Lc Rt = 1.21.  
 NMR (400 MHz,  $CDCl_3$ ): 2.6 (3H, s,  $CH_3CO$ ); 3.86 (3H, s, MeO); 6.96 (2H, d,  
 $J = 8.5$  Hz, aryl-H); 7.3 (2H, d,  $J = 8.5$  Hz, aryl-H); 7.44 (1H, bs, NH); 7.72 ((1H,  
 d,  $J = 2$  Hz, aryl-H); 7.84 (1H, dd,  $J = 2$  and 8.5 Hz, aryl-H); 8.6 (1H, bd,  $J = 8.5$   
 Hz, aryl-H); 9.5 (1H, s, CHO).

15

Step 7) (R)-N-(1-Phenylethyl)-N-((4-acetamido-3-(4-methoxyphenyl)phenyl)methyl)amine:

The title compound was prepared from N-[4-formyl-2-(4-  
 20 methoxyphenyl)phenyl]acetamide and (R)- $\alpha$ -methylbenzylamine according to  
 general procedure C.

 $C_{24}H_{26}N_2O_2$ Mass (calculated): [374]; (found):  $[M+H^+] = 375$ .

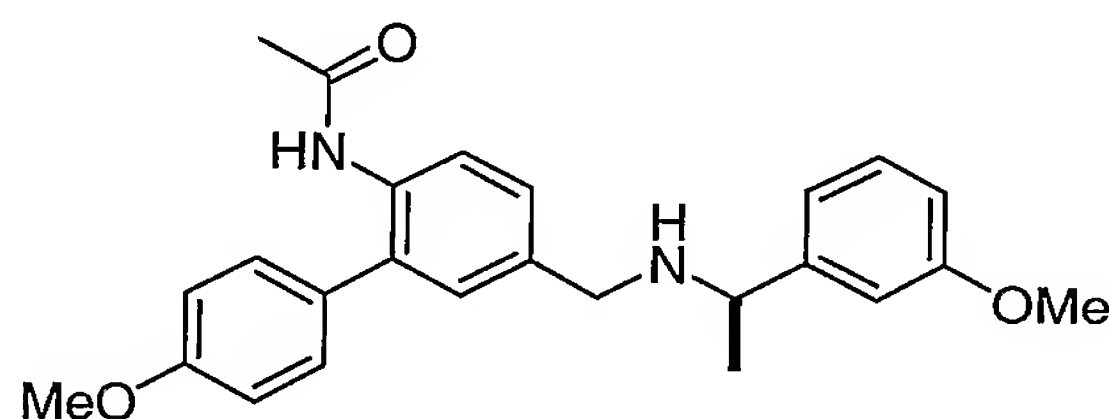
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NMR (400 MHz, CDCl<sub>3</sub>): 1.3 (3H, d,  $J = 6$  Hz, NCHCH<sub>3</sub>); 1.95 (3H, s, CH<sub>3</sub>CO); 3.5 and 3.55 (2H, dd,  $J = 12$  Hz, CH<sub>2</sub>N); 3.7 (1H, q,  $J = 6$  Hz, NCHMe); 3.75 (3H, s, MeO); 6.9 (2H, d,  $J = 8$  Hz, aryl-H); 7-7.1 (2H, m, aryl-H); 7.1-7.35 (7H, m, aryl-H); 8.1 (1H, d,  $J = 8$  Hz, aryl-H).

5

**Example 2**

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-acetamido-3-(4-methoxyphenyl)phenyl)methyl)amine



10 The title compound was prepared from N-[4-formyl-2-(4-methoxyphenyl)phenyl]acetamide and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

$C_{25}H_{28}N_2O_3$

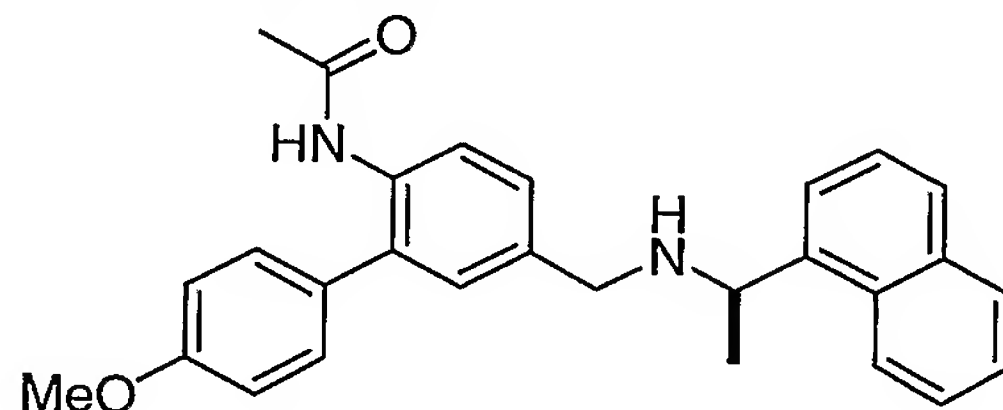
Mass (calculated): [404]; (found):  $[M+H^+] = 254, 405$ .

15 NMR (400 MHz, CDCl<sub>3</sub>): 1.3 (3H, d,  $J = 6$  Hz, NCHCH<sub>3</sub>); 1.95 (3H, s, CH<sub>3</sub>CO); 3.5 and 3.55 (2H, dd,  $J = 12$  Hz, CH<sub>2</sub>N); 3.7-3.75 (4H, m, MeO and NCHMe); 3.75 (3H, s, MeO); 6.7 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.75-6.8 (2H, m, aryl-H); 6.9 (2H, d,  $J = 8$  Hz, aryl-H); 7-7.1 (2H, m, aryl-H); 7.1-7.35 (3H, m, aryl-H); 8.1 (1H, d,  $J = 8$  Hz, aryl-H).

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**Example 3**

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-acetamido-3-(4-methoxyphenyl)phenyl)methyl)amine



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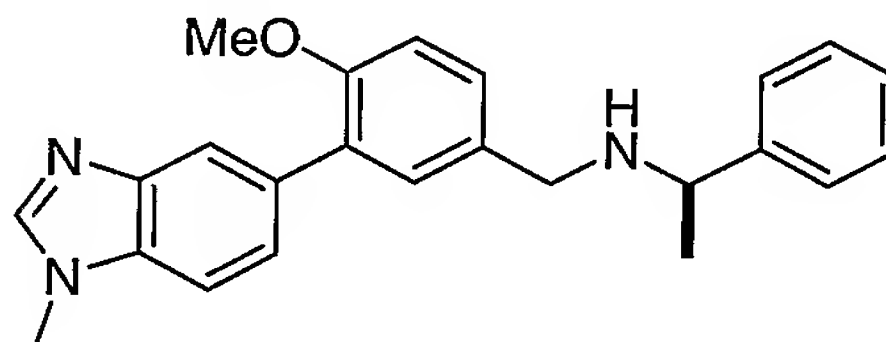
The title compound was prepared from N-[4-formyl-2-(4-methoxyphenyl)-phenyl]acetamide and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{28}H_{28}N_2O_2$

- 5 Mass (calculated): [424]; (found):  $[M+H^+] = 425, 254$ .  
NMR (400 MHz,  $CDCl_3$ ): 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 1.95 (3H, s,  $CH_3CO$ );  
3.6 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.8 (3H, s, MeO); 4.65 (1H, q,  $J = 6$  Hz,  
NCHMe); 6.9 (2H, d,  $J = 8$  Hz, aryl-H); 7.0-7.05 (2H, m, aryl-H); 7.1-7.15 (2H,  
m, aryl-H); 7.35-7.5 (3H, m, aryl-H); 7.7 (2H, d,  $J = 8$  Hz, aryl-H); 7.75-7.85 (1H,  
10 m, aryl-H); 8-8.05 (1H, m, aryl-H); 8.1 (1H, d,  $J = 8$  Hz, aryl-H).

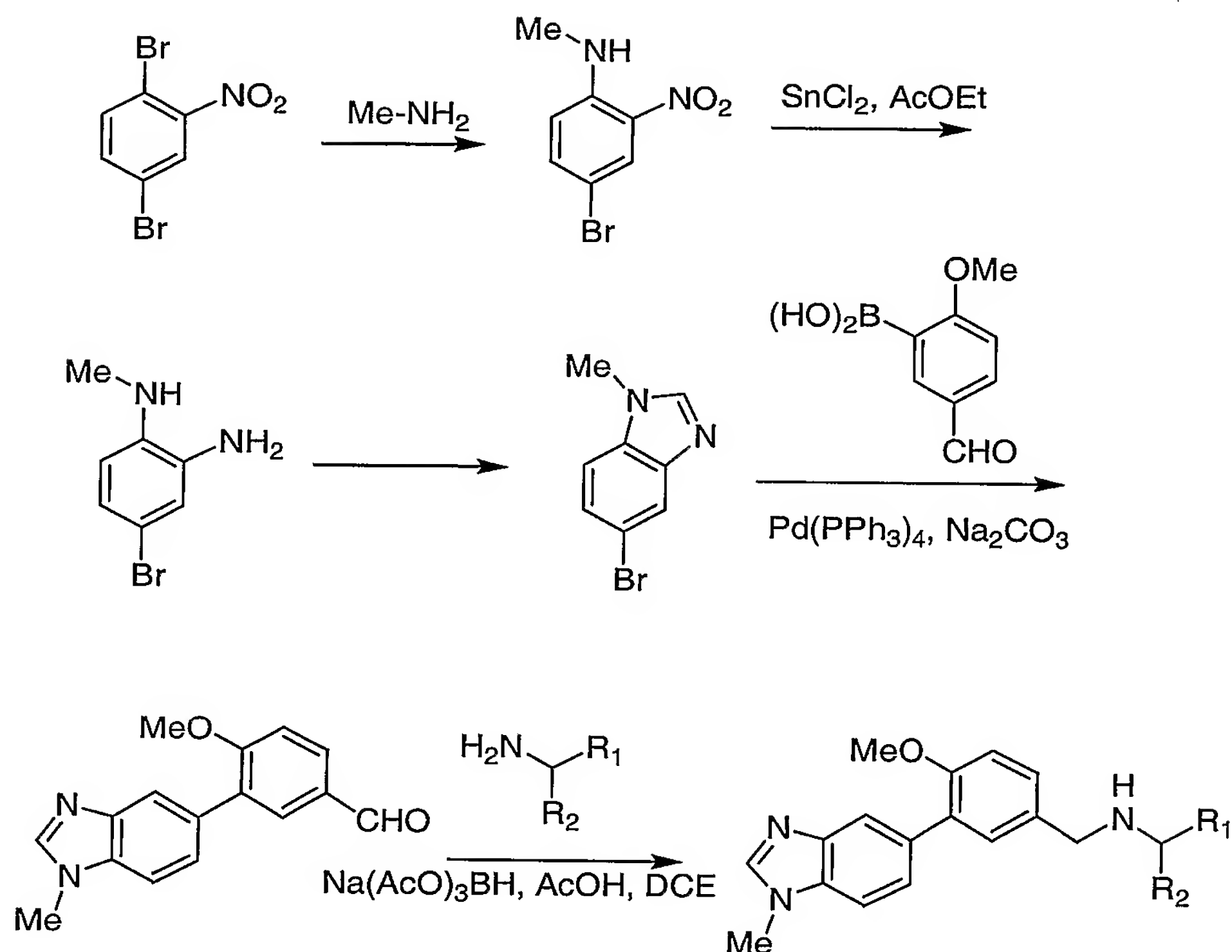
#### Example 4

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(1-methylbenzimidazol-5-yl)phenyl)methyl)amine

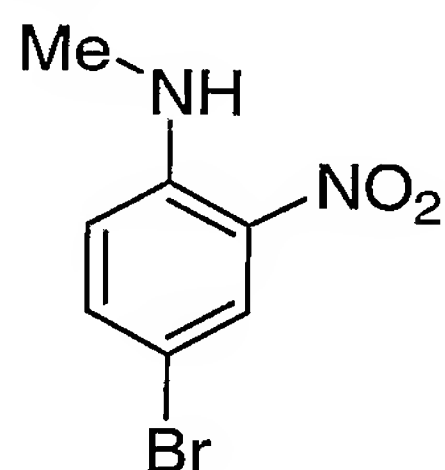


15

- 33 -



Step1) N-Methyl-4-bromo-2-nitroaniline/(4-Bromo-2-nitrophenyl)methylamine



5

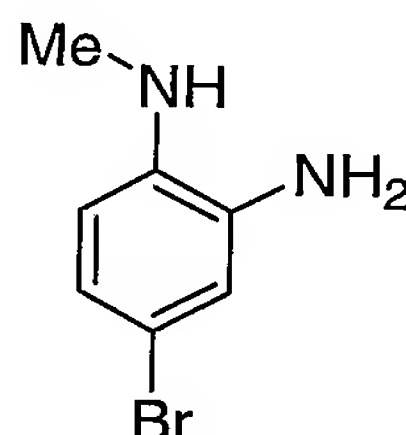
2,5-Dibromobenzene (5 g, 17.8 mmol) was added to a solution of methylamine (13.8 mL of a 40% aq. solution) and the mixture was stirred for 16 hours, then 8 mL of THF were added and the reaction was stirred for 2 hours at room temperature and then for further 2 hours at 50°C. The reaction mixture was then cooled and extracted twice into ethyl acetate. The solvent was removed under reduced pressure and the crude was chromatographed (silica, AcOEt 2-10% in hexane) to afford 2 g of orange crystals.



- 34 -

NMR (400 MHz, CDCl<sub>3</sub>): 2.95 (3H, d, ,  $J = 5$  Hz, NCH<sub>3</sub>); 3.92 (3H, s, MeN); 6.7 (d,  $J = 8.5$  Hz, aryl-H); 7.45 (1H, dd, ,  $J = 2$  and 8.5 Hz, aryl-H); 7.9 (1H, bs, NH); 8.2 (1H, d, ,  $J = 2$  Hz, aryl-H).

5 Step 2) 2-*N*-Methylamino-5-bromoaniline/(2-Amino-4-bromophenyl)methylamine

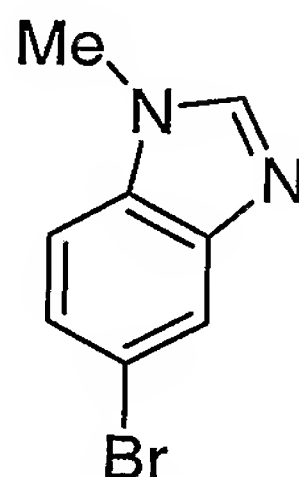


10 A solution of the nitroaniline from Step 1 (1.56 g, 6.75 mmol) and tin(II) chloride (7.62 g, 33.7 mmol) in ethyl acetate (40 mL) was refluxed under nitrogen for 3 hours. The mixture was then poured onto ice, neutralized with saturated NaHCO<sub>3</sub> and extracted into ethyl acetate. The organic layer was washed with brine and dried over sodium sulphate to afford 1.5 g of crude red oil which was used without further purification.

C<sub>7</sub>H<sub>9</sub>BrO<sub>2</sub> Mass (calculated): [201.07]; (found): [M+] = 201 (bromine).

15 NMR (400 MHz, MeOH-d<sub>4</sub>): 3.88 (3H, s, MeO); 2.8 (3H, s, MeN); 6.7 (1H, d,  $J = 8.5$  Hz, aryl-H); 6.85 (1H, dd, ,  $J = 2$  and 8.5 Hz, aryl-H); 6.9 (1H, d, ,  $J = 2$  Hz, aryl-H).

Step 3) 5-Bromo-1-methylbenzimidazole:



20 A solution of 2-*N*-methylamino-5-bromoaniline (1 g, 4.97 mmol) in triethyl orthoformate (30 mL) was refluxed for 5 hours. The solvent was removed under reduced pressure to afford 1 g of the title bromobenzimidazole.

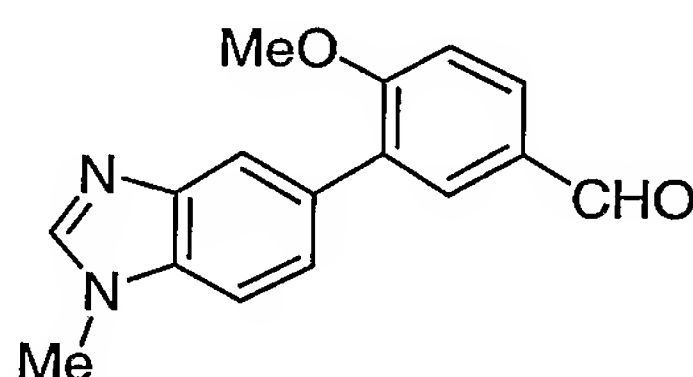
- 35 -

$C_8H_7BrN_2$  Mass (calculated): [211.06]; (found):  $[M^+] = 211$  (bromine).

NMR (400 MHz,  $MeOH-d_4$ ): 3.88 (3H, s, MeO); 2.8 (3H, s, MeN); 6.7 (1H, d,  $J = 8.5$  Hz, aryl-H); 6.85 (1H, dd,  $J = 2$  and 8.5 Hz, aryl-H); 6.9 (1H, d,  $J = 2$  Hz, aryl-H).

5

Step 4) 4-Methoxy-3-(1'-methylbenzimidazol-5'-yl)benzenecarboxaldehyde/4-Methoxy-3-(1-methylbenzimidazol-5-yl)benzaldehyde:



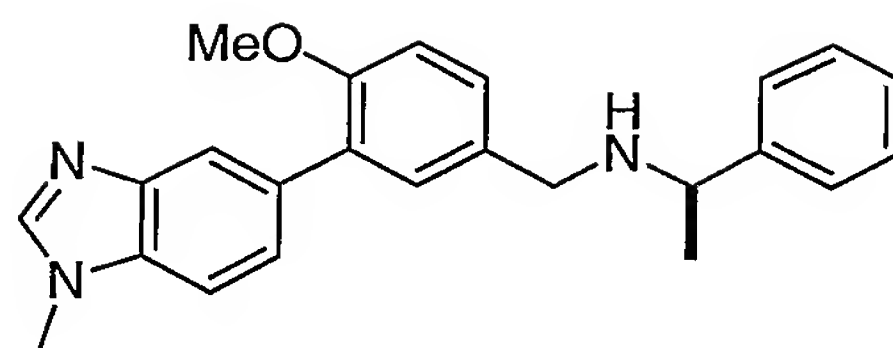
10 To a degassed solution of 5-bromo-1-methylbenzimidazole (0.56 g, 2.63 mmol), 5-formyl-2-methoxybenzeneboronic acid (0.57 g, 3.2 mmol) and potassium carbonate (0.91 g, 6.6 mmol) in toluene/ethanol 2/1 (30 mL) a catalytic amount of  $Pd(PPh_3)_4$  (0.03 g, 1 mmol%) was added and the solution was degassed for further 5 minutes. The mixture was refluxed for 5 hours. The residue was extracted into  
15 ethyl acetate and washed with water and then saturated brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the crude was purified by column (silica, EtOAc to 5% MeOH in AcOEt) to afford 0.6 g of product.

$C_8H_7BrN_2$

20 Mass (calculated): [266.30]; (found):  $[M^+] = 267$ .  
NMR (400 MHz,  $CDCl_3$ ): 3.88 (3H, s, MeO); 3.92 (3H, s, MeN); 7.12 (1H, d,  $J = 8.5$  Hz, aryl-H); 7.4-7.5 (2H, m, aryl-H); 7.8-7.95 (3H, m, aryl-H); 7.98 (1H, s, imidazole N=CHN); 9.95 (1H, s, CHO).

25 Step 5) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(1-methylbenzimidazol-5-yl)phenyl)methyl)amine

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The title compound was prepared from 4-methoxy-3-(1-methylbenzimidazol-5-yl)benzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

5  $C_{24}H_{25}N_3O$

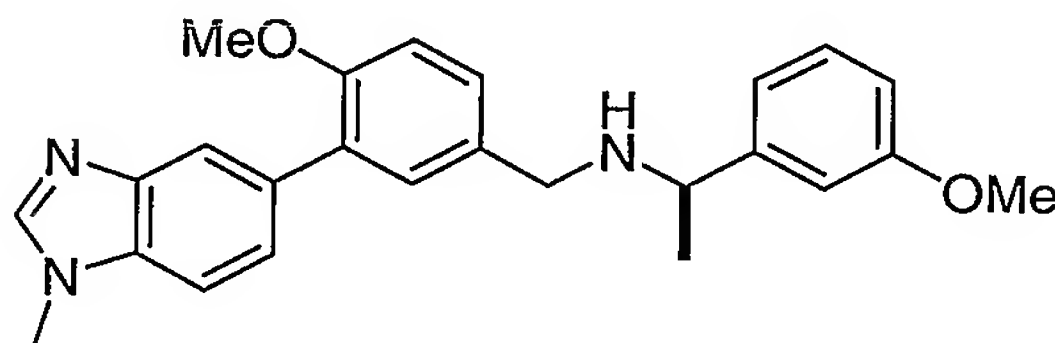
Mass (calculated): [371]; (found):  $[M+H^+] = 251, 372, 268$ .

NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7 (3H, s, NMe); 3.75-3.85 (4H, m and s,  $NCHMe$  and MeO); 6.9 (2H, d,  $J = 8$  Hz, aryl-H); 7.25-7.3 (3H, m, aryl-H); 7.3-7.4 (5H, m, aryl-H);  
 10 7.45 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.8 (1H, aryl-H); 7.9 (1H, m, aryl-H).

### Example 5

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(1-methylbenzimidazol-5-yl)phenyl)methyl)amine

15



The title compound was prepared from 4-methoxy-3-(1-methylbenzimidazol-5-yl)benzaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

20  $C_{25}H_{27}N_3O_2$

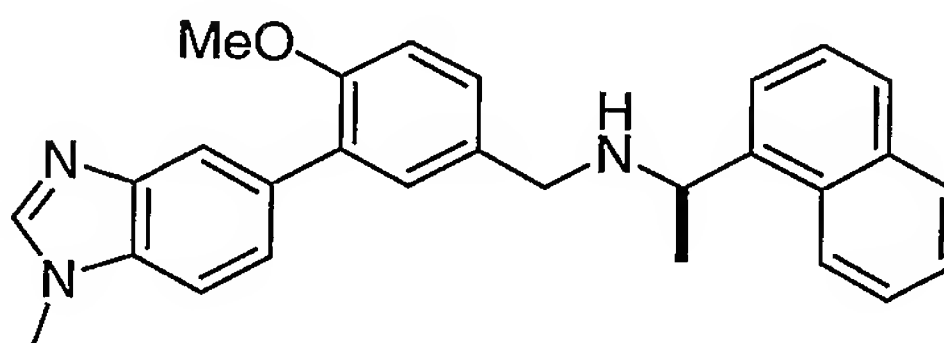
Mass (calculated): [401]; (found):  $[M+H^+] = 402, 251, 268$ .

NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7-3.9 (10H, m and 2s,  $NCHMe$ , NMe and MeO); 6.7 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.85-6.95 (3H, m, aryl-H); 7.15-7.3 (3H, m, aryl-H); 7.35  
 25 (1H, m, aryl-H); 7.45 (1H, m, aryl-H); 7.8-7.95 (2H, m, aryl-H).

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**Example 6**

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(1-methylbenzimidazol-5-yl)phenyl)methyl)amine



5

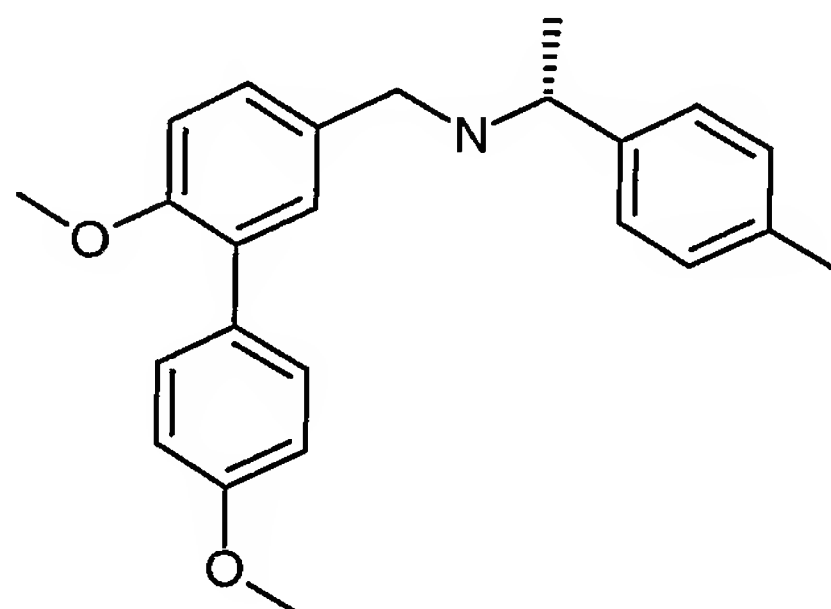
The title compound was prepared from 4-methoxy-3-(1-methylbenzimidazol-5-yl)benzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{28}H_{27}N_3O$

- 10 Mass (calculated): [371]; (found):  $[M+H^+] = 155, 422, 268, 251$ .  
 NMR (400 MHz,  $CDCl_3$ ): 1.6 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6-3.7 (4H, m,  $CH_2N$  and Nme); 3.7-3.8 (4H, m,  $CH_2N$  and MeO); 4.8 (1H, q,  $J = 6$  Hz,  $NCHCH_3$ ); 6.8 (1H, d,  $J = 8$  Hz, aryl-H); 7.15 (1H, d,  $J = 1$  Hz, aryl-H); 7.2-7.3 (1H, m, aryl-H); 7.3-7.35 (2H, m, aryl-H); 7.35-7.5 (2H, m, aryl-H); 7.5 (1H, t,  $J = 7$  Hz, aryl-H);  
 15 7.7 (1H, d,  $J = 8$  Hz, aryl-H); 7.8-7.95 (5H, m, aryl-H).

**Example 7**

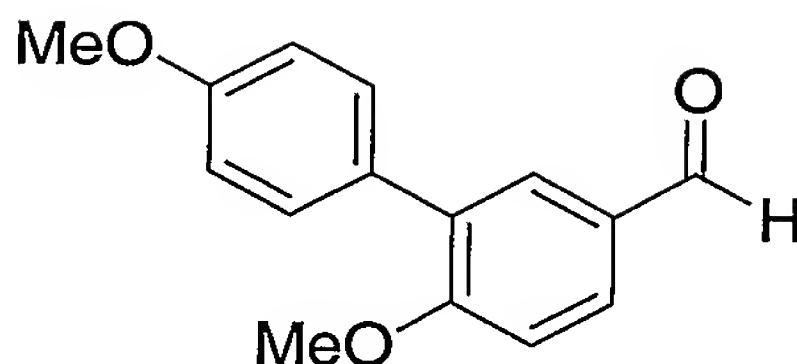
(R)-N-(1-(4-Methylphenyl)ethyl)-N-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



20

Step 1) 4-Methoxy-3-(4-methoxyphenyl)benzaldehyde

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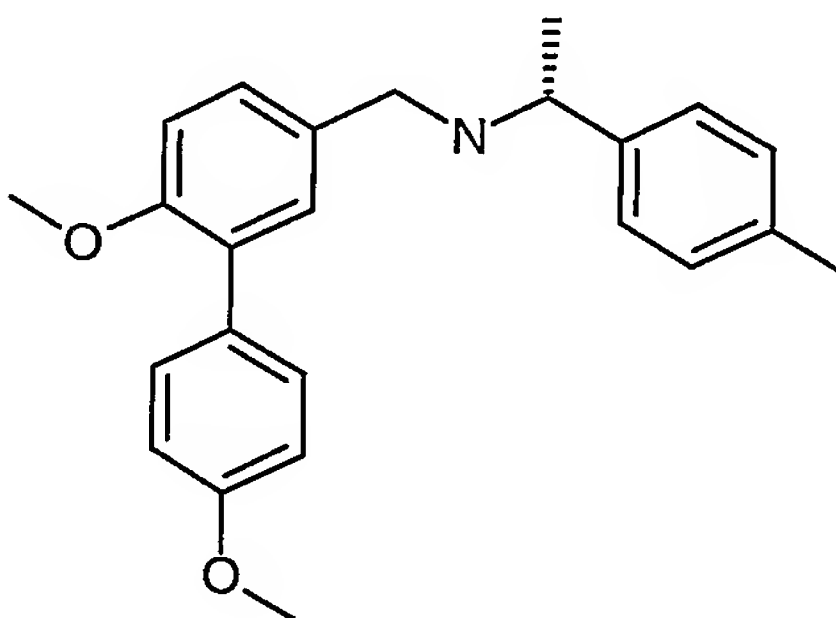


3-Bromo-4-methoxybenzaldehyde (1.92 g, 9 mmol, Aldrich) and 4-methoxyphenylboronic acid (1.52 g, 10 mmol, Aldrich) were dissolved in ethylene glycol dimethyl ether (15 mL, Aldrich). To the solution was added lithium chloride (0.72 g, 30 mmol, Aldrich) and aqueous 2 M sodium carbonate solution (15 mL, 30 mmol). After the mixture was bubbled with nitrogen for 10 min at room temperature, tetrakis(triphenylphosphine)palladium(0) (1.15 g, 1.0 mmol, Aldrich) was added to the mixture. The mixture was stirred under nitrogen at 80 C for overnight then the reaction was cooled at room temperature and diluted in ethyl acetate (50 mL). The solid portion was filtered out through Celite pad. The organic phase was separated and washed by water (30 mL) and brine (30 mL). The resulting organic layer was dried over anhydrous magnesium sulfate and concentrated via vacuo. The title compound was purified by column chromatography (silica gel, hexane/ethyl acetate 5/1) to give the title compound as white solid in 88% yield (2.12 g, 8.8 mmol).

$C_{15}H_{14}O_3$

MS (ESI, pos. ion) m/z: 243.1 (M+1); MS (ESI, neg. ion) m/z: 241.0 (M-1).

Step 2) (R)-N-(1-(4-Methylphenyl)ethyl)-N-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine





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The title compound was prepared from 4-methoxy-3-(4-methoxyphenyl)-benzaldehyde and (R)-4-methyl- $\alpha$ -methylbenzylamine according to general procedure A.

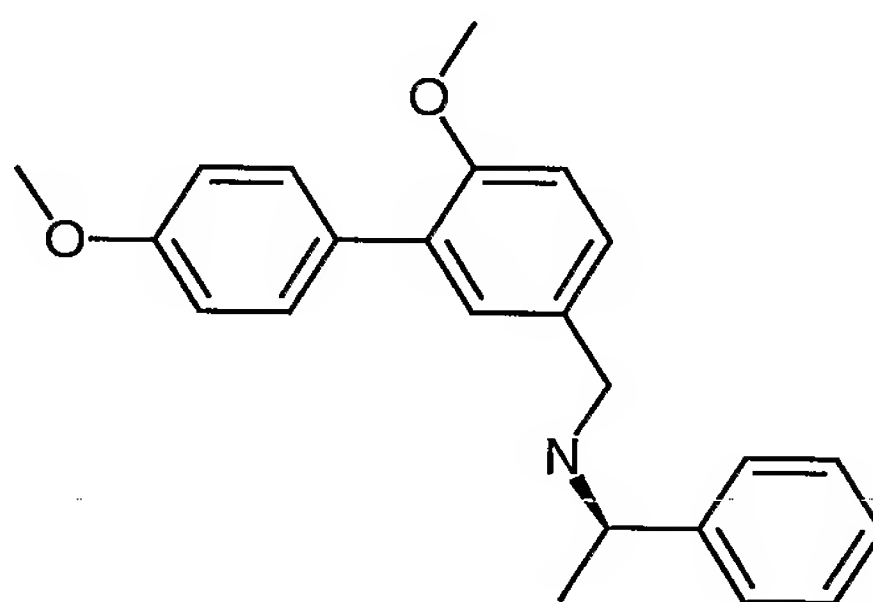
$C_{24}H_{27}NO_2$

- 5 Mass (calculated): [361]; (found):  $[M+H^+] = 262$ ;  
NMR (400 MHz, MeOH- $d_4$ ): 1.55 (3H, d,  $J=7$  Hz, NCHCH<sub>3</sub>); 2.5 (3H, s, aryl-CH<sub>3</sub>) 3.65 and 3.75 (2H, dd,  $J=12$  Hz, CH<sub>2</sub>N); 3.9 (3H, s, MeO); 3.9 (1H, m, NCHMe); 3.95 (3H, s, MeO); 7.05-7.15 (3H, m, aryl-H); 7.3-7.45 (6H, m, aryl-H); 7.62 (2H, d,  $J=7$  Hz, aryl-H).

10

### Example 8

(R)-*N*-(1-Phenylethyl)-*N*-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



- 15 The title compound was prepared from 4-methoxy-3-(4-methoxyphenyl)-benzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure A.

$C_{23}H_{25}NO_2$

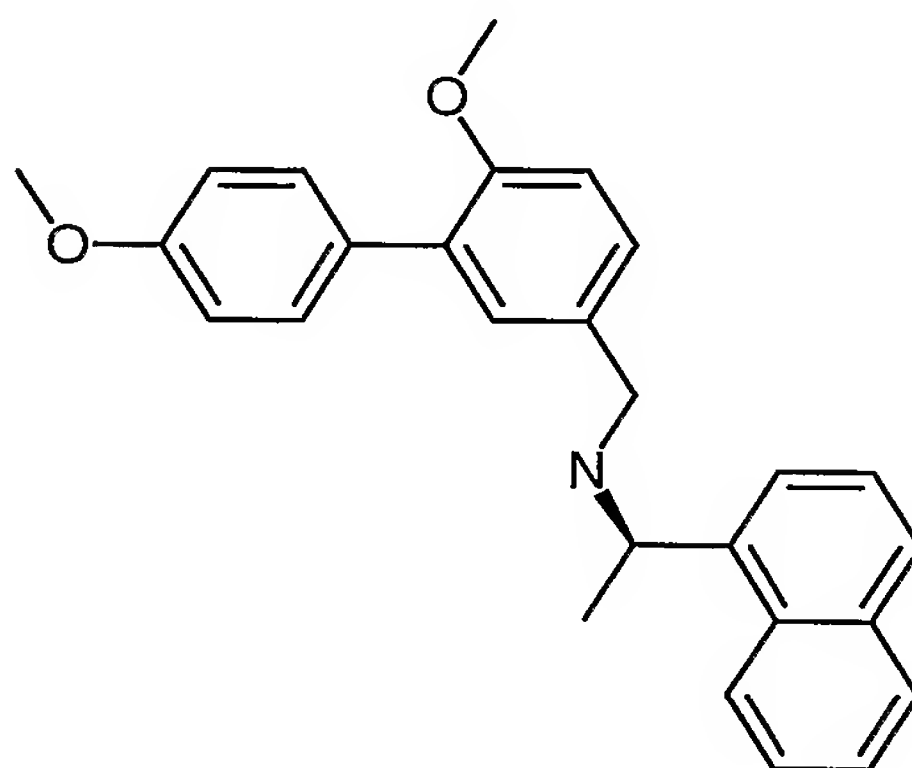
Mass (calculated): [347]; (found):  $[M+H^+] = 348$ .

- 20 NMR (400 MHz, MeOH- $d_4$ ): 1.55 (3H, d,  $J=7$  Hz, NCHCH<sub>3</sub>); 2.5 (3H, s, aryl-CH<sub>3</sub>) 3.65 and 3.75 (2H, dd,  $J=12$  Hz, CH<sub>2</sub>N); 3.9 (3H, s, MeO); 3.9 (1H, m, NCHMe); 3.95 (3H, s, MeO); 7.05-7.15 (3H, m, aryl-H); 7.3-7.45 (6H, m, aryl-H); 7.62 (2H, d,  $J=7$  Hz, aryl-H).

25

### Example 9

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(4'-methoxyphenyl)-phenyl)methyl)amine



5

The title compound was prepared from 4-methoxy-3-(4-methoxyphenyl)-benzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure A.

$$\text{C}_{27}\text{H}_{27}\text{NO}_2$$

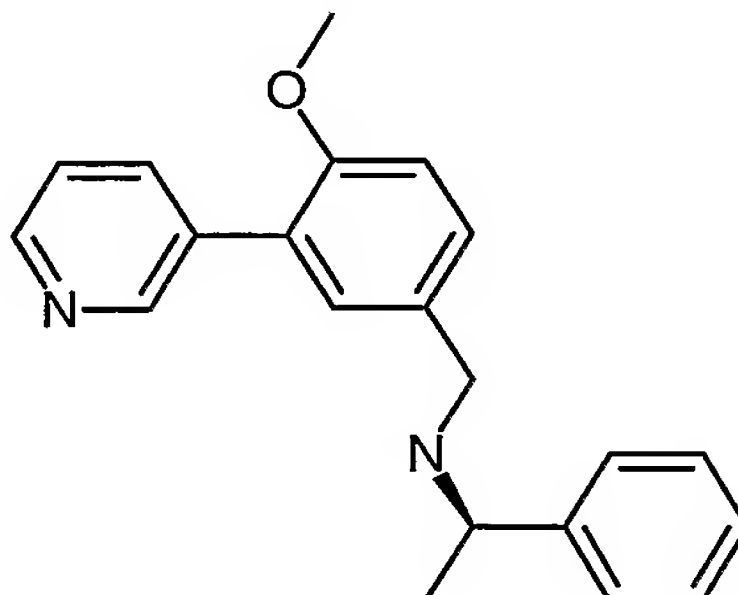
10 Mass (calculated): [397]; (found):  $[M+H^+] = 398$ .

NMR (400 MHz, MeOH-d<sub>4</sub>): 1.65 (3H, d,  $J=7$  Hz, NCHCH<sub>3</sub>); 3.8 and 3.85 (2H, dd,  $J=15$  Hz, CH<sub>2</sub>N); 3.9 (3H, s, MeO); 4 (3H, s, MeO); 3.9 (1H, m, NCHMe); 4.85 (1H, q,  $J=7$  Hz, NCHMe); 7.05 (2H, d,  $J=7$  Hz, aryl-H); 7.15 (1H, d,  $J=7$  Hz, aryl-H); 7.25 (1H, d,  $J=1$  Hz, aryl-H); 7.35 (1H, dd,  $J=1$  and 7 Hz, aryl-H); 7.5 (2H, d,  $J=7$  Hz, aryl-H); 7.55-7.7 (2H, m, naphthyl-H); 7.7 (1H, t,  $J=7$  Hz, naphthyl-H); 7.9 (1H, d,  $J=7$  Hz, naphthyl-H); 7.95 (1H, d,  $J=7$  Hz, naphthyl-H); 8.05 (1H, d,  $J=7$  Hz, naphthyl-H); 8.15 (1H, d,  $J=7$  Hz, naphthyl-H).

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**Example 10**

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-3-yl)phenylmethyl)amine



The title compound was prepared from 4-methoxy-3-(3-pyridyl)benzaldehyde and  
5 (R)- $\alpha$ -methylbenzylamine according to general procedure A.

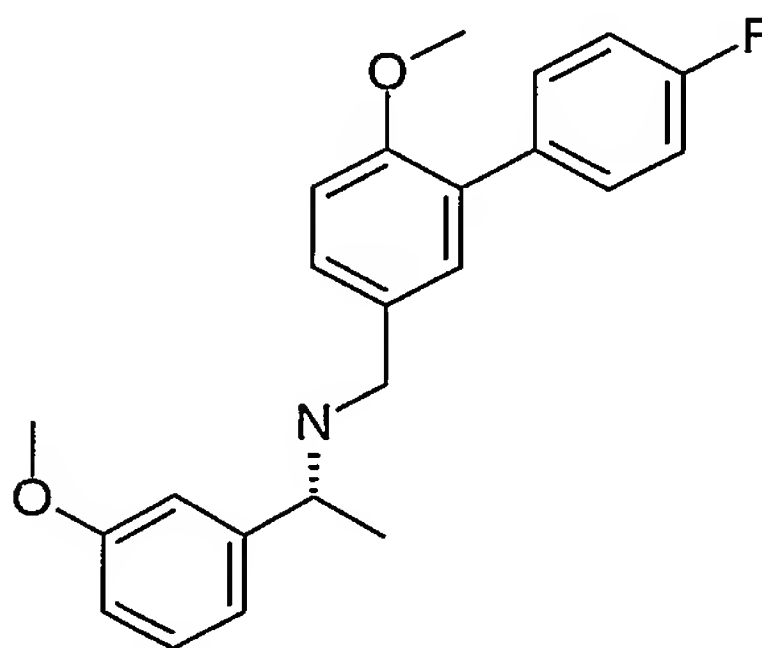
$C_{21}H_{22}N_2O$

Mass (calculated): [318]; (found):  $[M+H^+] = 319, 198$ .

NMR (400 MHz, MeOH- $d_4$ ): 1.75 (3H, d,  $J=7$  Hz, NCHCH<sub>3</sub>); 3.92 (3H, s, MeO);  
3.55 and 4.2 (2H, dd,  $J=10$  Hz, CH<sub>2</sub>N); 4.5 (1H, q,  $J=4.5$  Hz, NCHMe); 3.95  
10 (3H, s, MeO); 7.3 (1H, d,  $J=7$  Hz, aryl-H); 7.45-7.65 (7H, m, aryl-H); 8.05 (1H,  
bt, pyridyl-H); 7.75 (1H, d,  $J=7$  Hz, pyridyl-H); 8.8 (1H, bs, pyridyl-H); 9.05  
(1H, bs, pyridyl-H).

**Example 11**

15 (R)-N-(1-((3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(4'-fluorophenyl)-  
phenylmethyl)amine



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The title compound was prepared from 3-(4-fluorophenyl)-4-methoxybenzaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

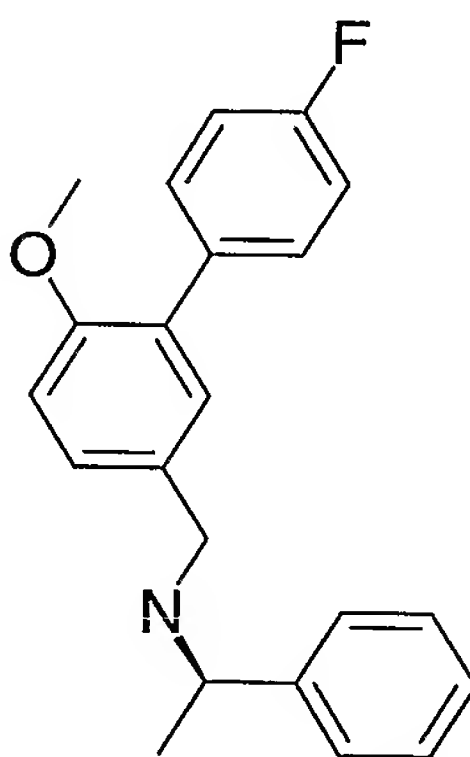
$C_{23}H_{24}FNO_2$  Mass (calculated): [365]; (found):  $[M+H^+] = 366$ , 215 base peak

5 NMR (400 MHz,  $CDCl_3$ ): 1.4 (3H, d,  $J=7$  Hz,  $NCHCH_3$ ); 3.65 and 3.75 (2H, dd,  $J=12$  Hz,  $CH_2N$ ); 3.82 (3H, s, MeO); 3.85 (3H, s, MeO); 3.8-3.9 (1H, m,  $NCHMe$ ); 6.85 (1H, dd,  $J=7$  and 2 Hz, aryl-H); 6.9-7.0 (3H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.2-7.35 (3H, m, aryl-H); 7.5-7.55 (2H, m, aryl-H).

10

### Example 12

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(4'-fluorophenyl)phenyl)methyl)amine



The title compound was prepared from 3-(4-fluorophenyl)-4-methoxybenzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

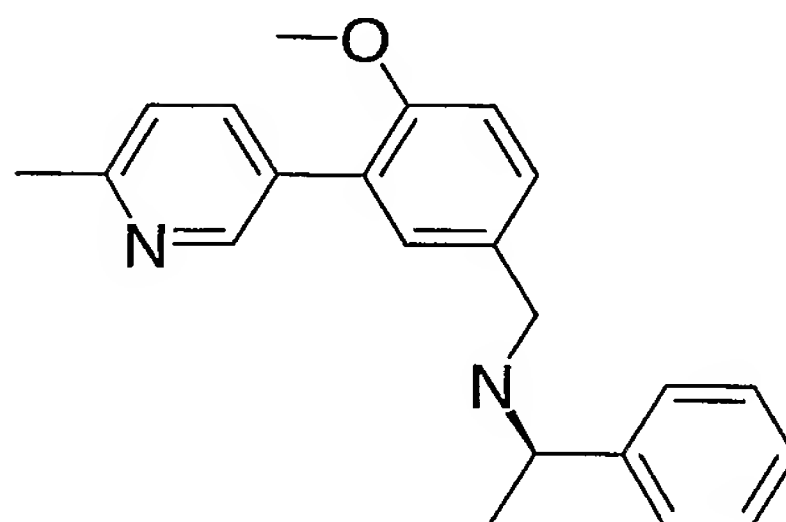
$C_{22}H_{22}FNO$  Mass (calculated): [335]; (found):  $[M+H^+] = 336$ , 215 base peak

15 NMR (400 MHz,  $CDCl_3$ ): 1.35 (3H, d,  $J=7$  Hz,  $NCHCH_3$ ); 3.5 and 3.6 (2H, dd,  $J=11$  Hz,  $J=7$  Hz;  $CH_2N$ ); 3.7 (3H, s, MeO); 4.82 (1H, q,  $J=7$  Hz;  $NCHMe$ ); 6.85 (1H, d,  $J=7$ , aryl-H); 7.0 (2H, t,  $J=7$  Hz; aryl-H); 7.15 (1H, d,  $J=2$  Hz, aryl-H);  
20 7.15-7.25 (2H, m, aryl-H); 7.25-7.35 (4H, m, aryl-H); 7.5 (2H, dd,  $J=7$  and 6 Hz, aryl-H).

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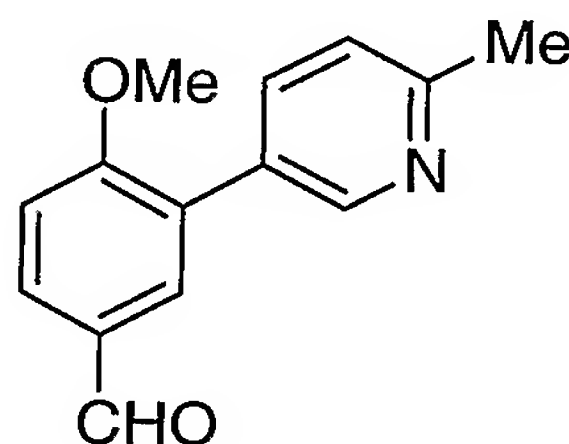
**Example 13**

R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2'-methylpyrid-5'-yl)phenylmethyl)-amine



5 (

Step 1) 4-Methoxy-3-(1-methylpyrid-5-yl)benzenecarboxaldehyde:

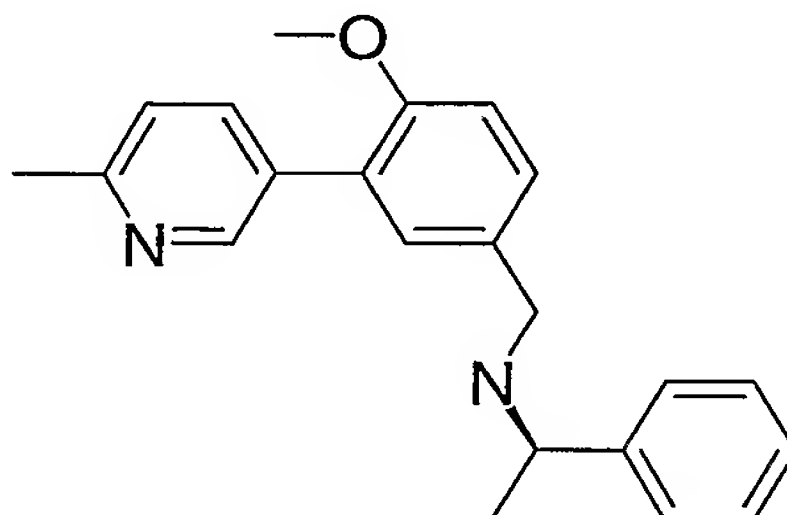


- 10 To a degassed solution of 5-bromo-2-methylpyridine (2.75 g, 15 mmol) and potassium carbonate (4.5 g, 33 mmol) in toluene (70 mL) a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.17 g, 0.15 mmol) was added and the solution was degassed for further 5 minutes. A degassed solution of 5-formyl-2-methoxybenzeneboronic acid (prepared according to Keseru, G.M. *et al. Tetrahedron* (48), 2, 913-922
- 15 (1992))(2.7 g, 15 mmol) in ethanol (30 mL) was then added and the mixture was refluxed for 15 hours. The residue was extracted into ethyl acetate and washed with saturated sodium bicarbonate solution and dried over sodium sulphate. The solvent was removed under reduced pressure and the crude was purified by column chromatography (silica, THF/DCM 2/1) to afford 2 g of pale yellow solid.
- 20 C<sub>14</sub>H<sub>13</sub>NO<sub>2</sub> Mass (calculated) [227]; (found) [M+H<sup>+</sup>] = 228; Lc Rt = 1.0, 92%. NMR (400 MHz, MeOH-d<sub>4</sub>): 2.65 (3H, s, Me-pyridine); 4.05 (3H, s, MeO); 7.35 (1H, d, J=10Hz, pyridyl-H); 7.45 (1H, 2, J=7Hz, aryl-H); 7.95 (1H, m, pyridyl-H); 8 (1H, d, J=2Hz ; aryl-H); 8.1 (1H, dd, J=2 and 7 Hz, aryl-H); 8.65 (1H, d, J=2Hz, -H); 10 (1H, s, CHO).



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Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2'-methylpyrid-5'-yl)-phenylmethyl)-amine



5

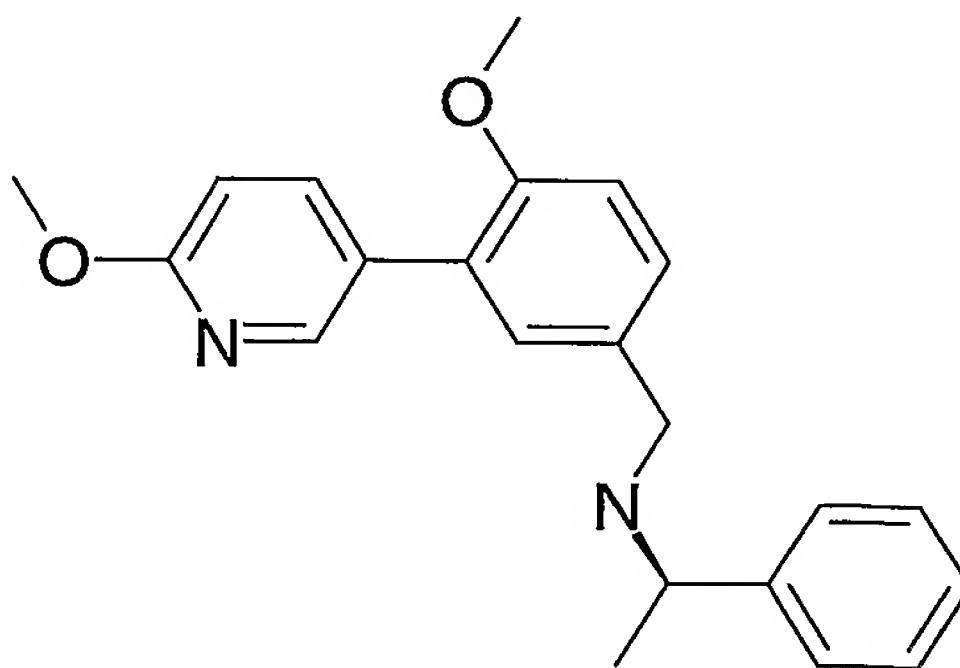
The title compound was prepared from 4-methoxy-3-(1-methylpyrid-5-yl)-benzenecarboxaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

$C_{22}H_{24}N_2O$  Mass (calculated): [332]; (found): ):  $[M+H^+] = 333$  NMR (400 MHz,  $CDCl_3$ ): 1.4 (3H, d,  $J=6.5$  Hz,  $NCHCH_3$ ); 2.65 (3H, s, pyridyl- $CH_3$ ); 3.61 and 3.67 (2H, dd,  $J = 13$  Hz,  $CH_2N$ ); 3.82 (3H, s, MeO); 3.86 (1H, q,  $J=6.5$  Hz,  $CH_3CH$ ); 6.45 (1H, d,  $J=8.5$  Hz); 7.2-7.35 (4H, m, aryl-H); 7.35-7.4 (4H, m, aryl-H); 7.77 (dd, 1H,  $J=2.2$  and 8.1 Hz, aryl-H); 8.66 (1H, d,  $J=1.8$  Hz, aryl-H).

15

**Example 14**

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2'-methoxypyrid-5'-yl)phenylmethyl)-amine



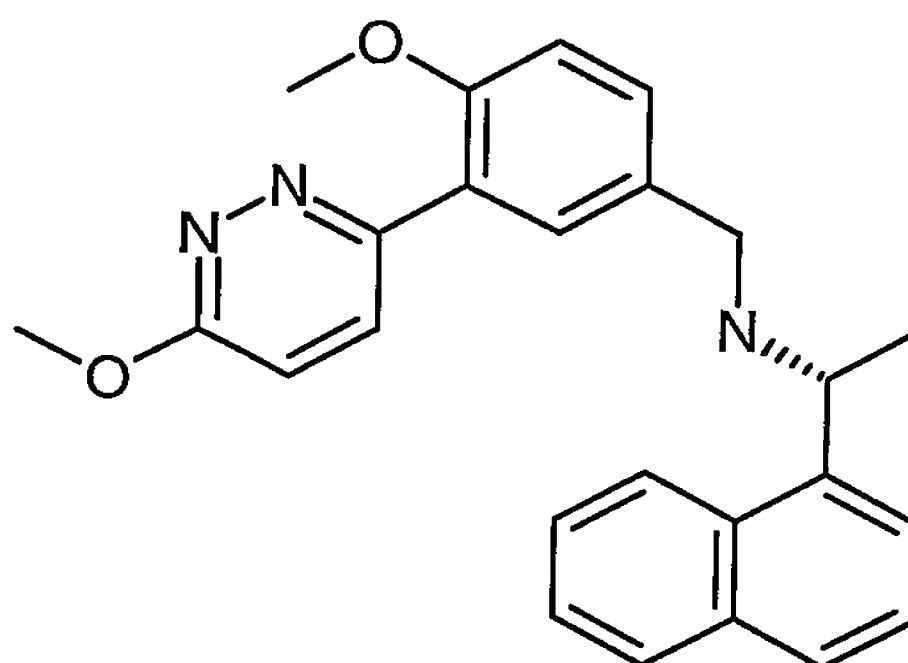
20 The title compound was prepared from 4-methoxy-3-(6-methoxy(3-pyridyl))-benzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

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$C_{22}H_{24}N_2O_2$  Mass (calculated): [348]; (found):  $[M+H^+] = 349$ , 228; NMR (400 MHz,  $CDCl_3$ ): 1.32 (3H, d,  $J = 6.8$  Hz,  $NCHCH_3$ ); 3.5 and 3.57 (2H, dd,  $J = 13$  Hz,  $CH_2N$ ); 3.72 (3H, s,  $OCH_3$ ); 3.78 (1H, q,  $J = 6.8$  Hz,  $CHCH_3$ ); 6.7 (1H, dd,  $J = 0.6$  and 8.6 Hz, aryl-H); 6.8 (1H, d,  $J = 8.4$  Hz, aryl-H); 7.10-6.35 (7H, m, aryl-H); 7.7 (1H, dd,  $J = 2.5$  and 8.6 Hz, aryl-H); 8.2 (1H, dd,  $J = 1.8$  and 8.2 Hz, aryl-H).

**Example 15**

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(6'-methoxypyridazin-3'-yl))phenylmethyl)amine

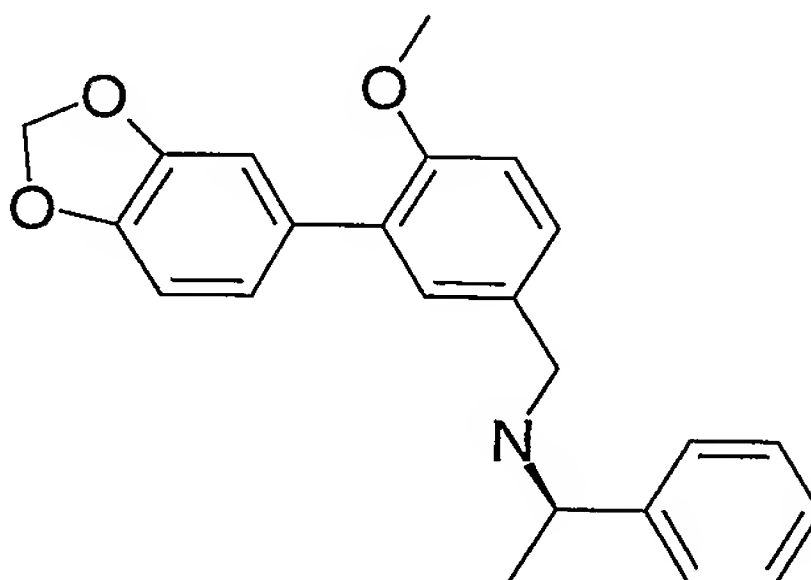


The title compound was prepared from 4-methoxy-3-(6-methoxypyridazin-3-yl)benzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure A.

$C_{25}H_{25}N_3O_2$  Mass (calculated): [399]; (found):  $[M+H^+] = 400$ ,  $[2M+H^+] = 799$ .

**Example 16**

(R)-N-(1-(Phenylethyl)-N-((4-methoxy-3-(3,4-methylenedioxyphenyl))phenylmethyl)amine



- 46 -

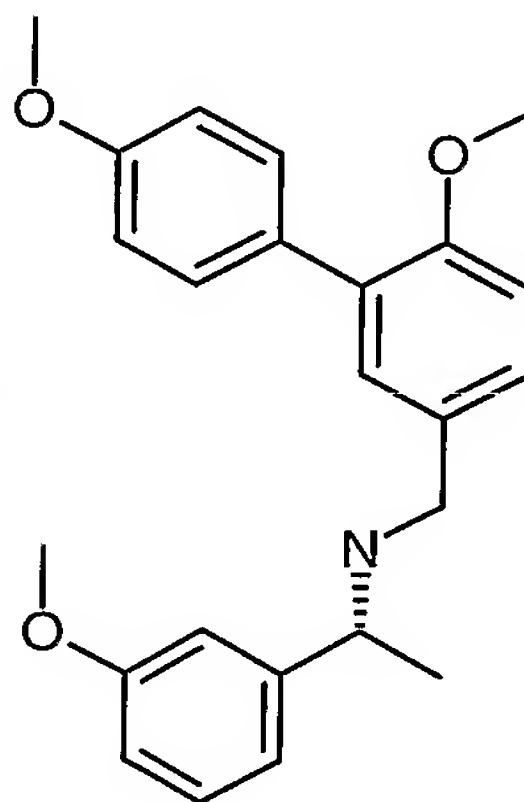
The title compound was prepared from 3-(2H-benzo[d]1,3-dioxolan-5-yl)-4-methoxybenzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure B.

5  $C_{23}H_{23}NO_3$  Mass (calculated): [361]; (found):  $[M+H^+] = 362$ , 241 NMR (400 MHz,  $CDCl_3$ ): 1.29 (3H, d,  $J = 6.8$  Hz,  $CHCH_3$ ); 3.50 and 3.54 (2H, dd,  $J = 13$  Hz,  $CH_2N$ ); 3.72 (3H, s,  $CH_3O$ ); 3.75 (1H, q,  $J = 6.8$  Hz,  $CHCH_3$ ); 5.90 (2H, s,  $OCH_2O$ ); 6.78 (1H, d,  $J = 7.7$  Hz, aryl-H); 6.83 (1H, d,  $J = 7.7$  Hz, aryl-H); 6.9 (1H, dd,  $J = 1.7$  and 7.7 Hz, aryl-H); 6.97 (1H, d,  $J = 1.7$  Hz, aryl-H); 7.10-7.15 (2H, m, aryl-H); 7.15-7.22 (1H, m, aryl-H); 7.24-7.31 (4H, m, aryl-H).

10

### Example 17

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



15

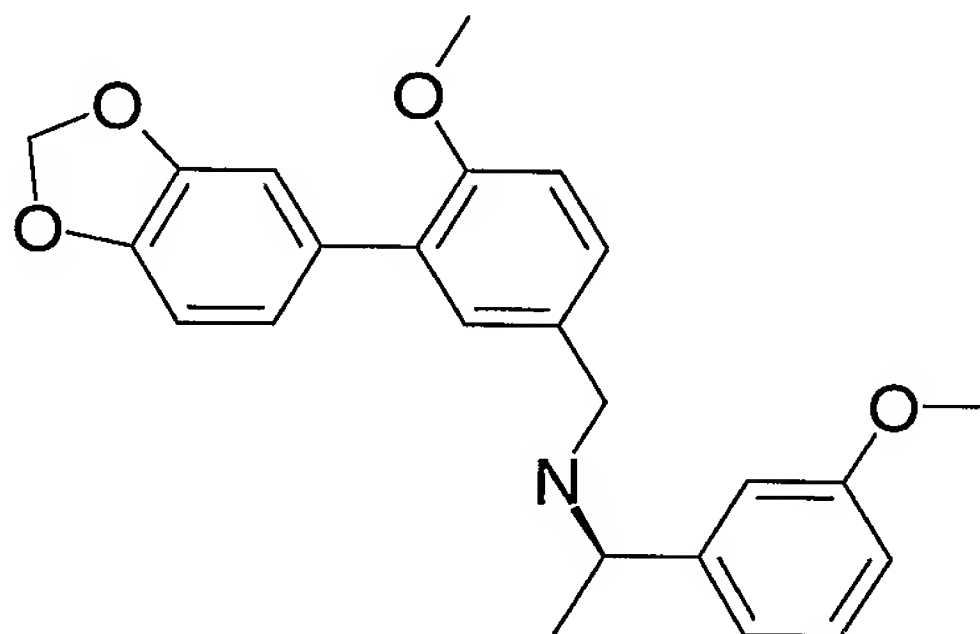
The title compound was prepared from 4-methoxy-3-(4-methoxyphenyl)-benzaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure A.

20  $C_{24}H_{27}NO_3$  Mass (calculated): [377]; (found):  $[M+H^+] = 378$ ,  $[M+MeCN + H^+] = 419$ .

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**Example 18**

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(4,5-methylenedioxyphenyl)phenyl)methyl)amine



5

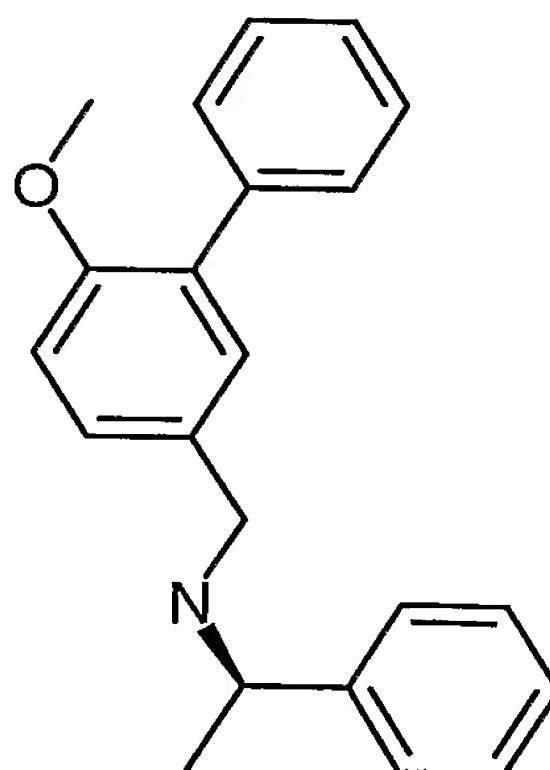
The title compound was prepared from 3-(2H-benzo[d]1,3-dioxolan-5-yl)-4-methoxybenzaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure B.

10  $C_{24}H_{25}NO_4$  Mass (calculated): [391]; (found):  $[M+H^+] = 392$ . NMR (400 MHz,  $CDCl_3$ ): 1.35 (3H, d,  $J = 6.8$  Hz,  $NCHCH_3$ ); 3.4-3.8 (9H, m,  $OCH_3$ ,  $OCH_3$ ,  $CHCH_3$ ,  $CH_2N$ ); 5.9 (2H, s,  $OCH_2O$ ); 6.7-7 (8H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H).

**Example 19**

15

(R)-N-(1-Phenylethyl)-N-(4-methoxy-3-phenyl)phenylmethyl)amine



The title compound was prepared from 4-methoxy-3-phenylbenzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure A.

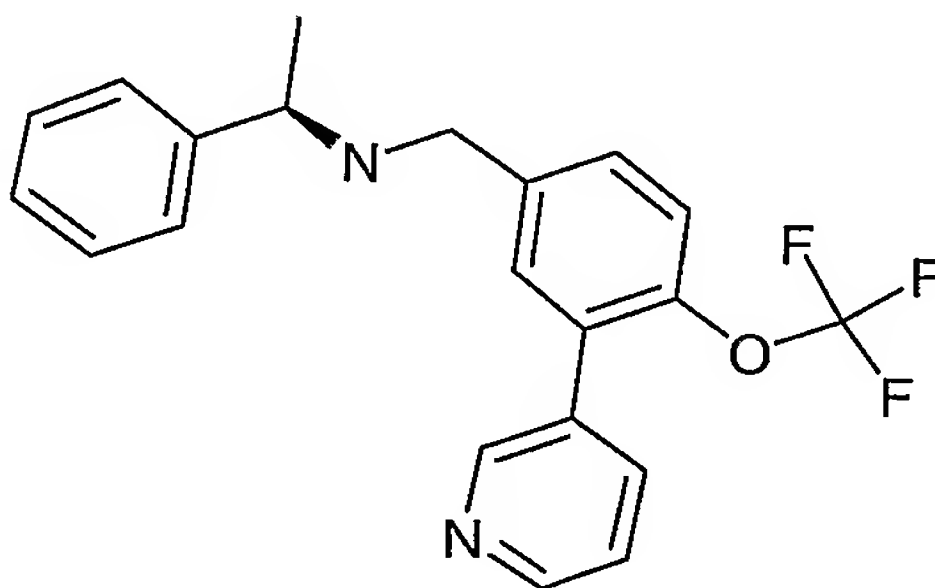
- 48 -

$C_{22}H_{23}NO$  Mass (calculated): [317]; (found):  $[M+H^+] = 318, 197$  (base peak).

**Example 20**

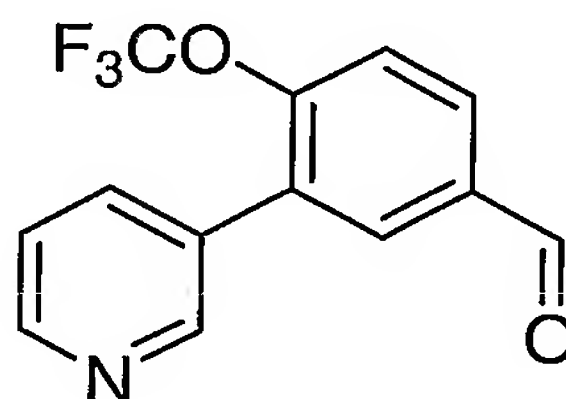
(R)-N-(1-Phenylethyl)-N-((4-trifluoromethoxy-3-(pyrid-3-yl)phenyl)methyl)amine

5



Step 1) 4-Trifluoromethoxy-3-(pyrid-3-yl)benzaldehyde

10



A solution of 3-chloro-4-trifluoromethoxybenzaldehyde (3 g, 13.3 mmol) and 3-pyridylboronic acid (1.97 g, 16.0 mmol) in dioxane (70 mL) and 2M  $K_2CO_3$  (20 mL) is degassed with nitrogen prior to addition of  $Pd(PPh_3)_4$  (1.5 g, 1.33 mmol). The mixture was stirred at 100°C under nitrogen for 40 hours, then cooled and filtered on celite/silica and the filtrate concentrated under reduced pressure. The crude was purified by column chromatography (2/1 heptane/ethyl acetate) to give 1.51 g of title compound.

$C_{13}H_8F_3NO_2$  Mass (calculated): [267]; (found)  $[M+H^+] = 268$  NMR (400 MHz,  $CDCl_3$ ): 7.3-7.35 (1H, m, aryl-H); 7.4-7.45 (1H, m, aryl-H); 7.7-7.75 (1H, m, aryl-H); 7.9-8 (2H, n, aryl-H); 8.65 (1H, bs, aryl-H); 8.7 (1H, bs, aryl-H).

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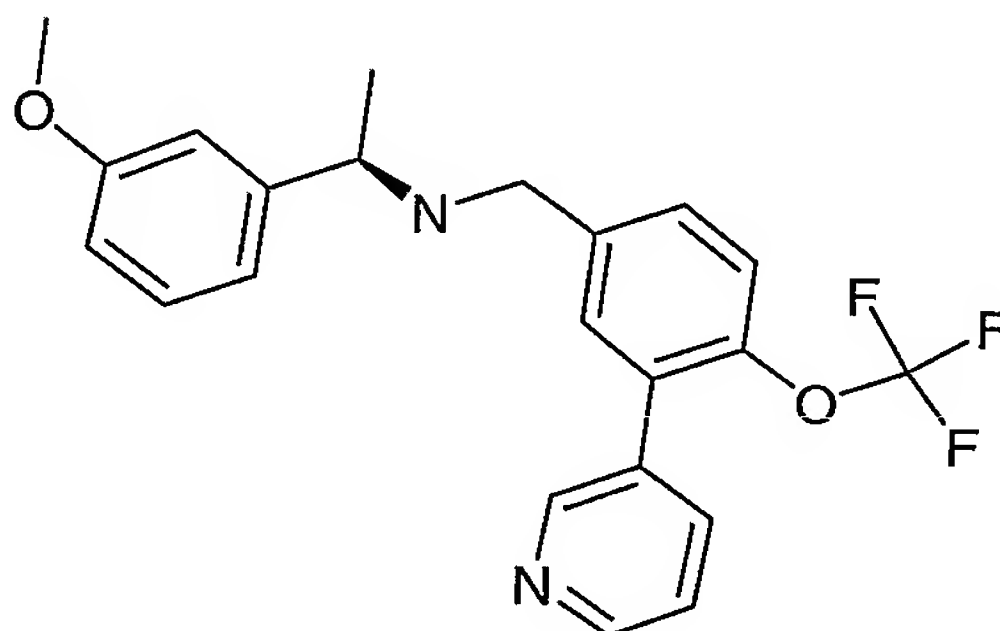
Step 2) (R)-N-(1-Phenylethyl)-N-((4-trifluoromethoxy-3-(pyrid-3-yl)phenylmethyl)amine

The title compound was prepared from 4-trifluoromethoxy-3-(pyrid-3-yl)benzenecarboxaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

$C_{21}H_{19}F_3N_2O$  Mass (calculated): [372]; (found):  $[M+H^+] = 373$  NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 (2H, s,  $CH_2N$ ); 3.8 (1H, q,  $J = 6$  Hz;  $NCHMe$ ); 7.20-7.40 (9H, m, aryl-H); 7.7 (1H, dt,  $J = 1$  and 8 Hz, aryl-H); 8.55 (1H, d,  $J = 3$  Hz, aryl-H); 8.65 (1H, bs, aryl-H).

**Example 21**

**(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-trifluoromethoxy-3-(pyrid-3-yl)phenylmethyl)amine**



The title compound was prepared from 4-trifluoromethoxy-3-(pyrid-3-yl)benzenecarboxaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

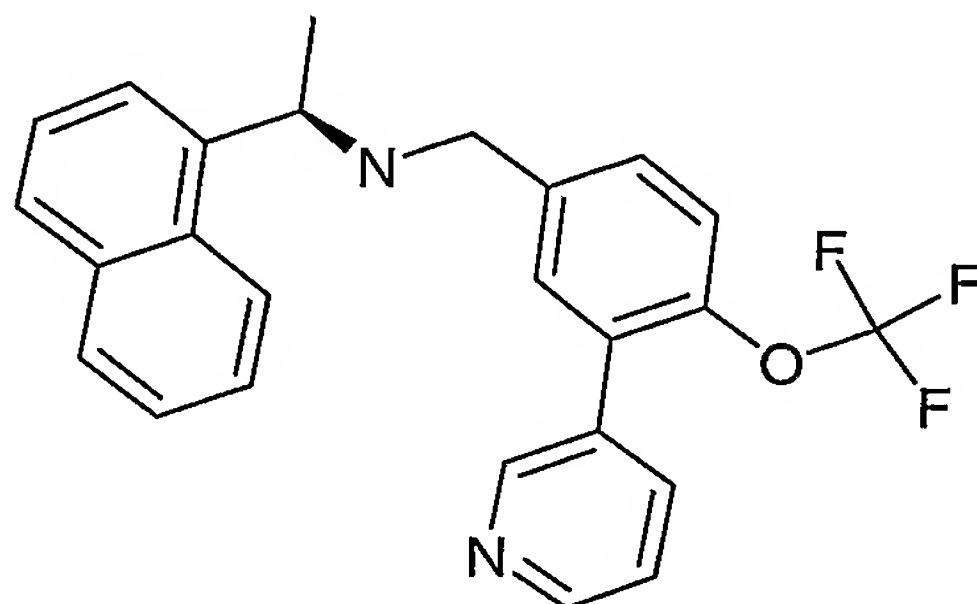
$C_{22}H_{21}F_3N_2O_2$  Mass (calculated): [402]; (found):  $[M+H^+] = 403$  NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 (2H, m,  $CH_2N$ ); 3.7-3.8 (4H, m,  $NCHMe$  and  $CH_3O$ ); 6.7 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.8-6.9 (2H, m, aryl-H); 7.20-7.40 (5H, m, aryl-H); 7.7 (1H, dt,  $J = 1$  and 8 Hz, aryl-H); 8.55 (1H, d,  $J = 3$  Hz, aryl-H); 8.65 (1H, bs, aryl-H).



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**Example 22**

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-trifluoromethoxy-3-(pyrid-3-yl)phenyl)methyl)amine



5

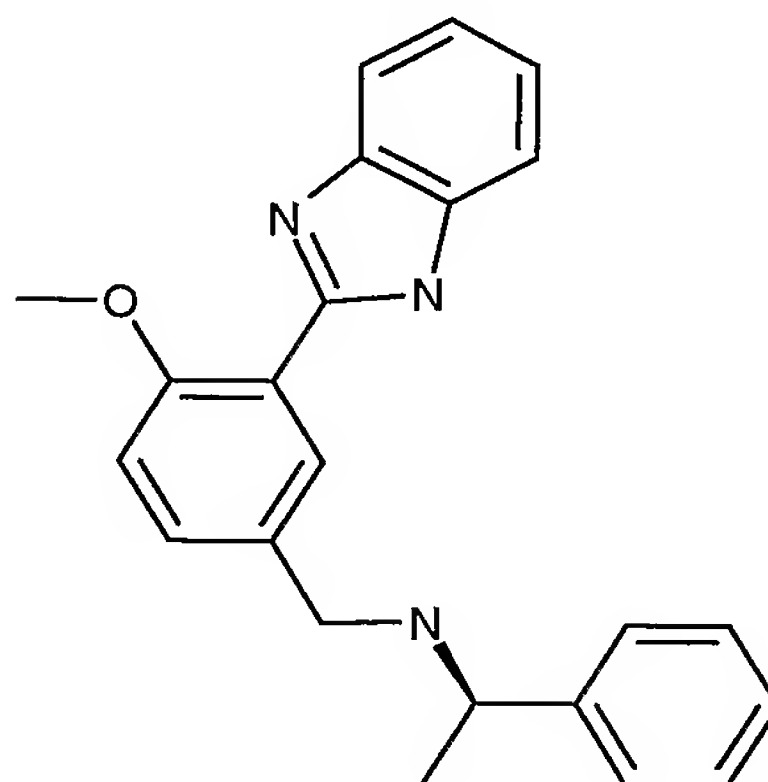
The title compound was prepared from 4-trifluoromethoxy-3-(pyrid-3-yl)benzene-carboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

C<sub>25</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O Mass (calculated): [422]; (found): [M+H<sup>+</sup>] = 423 NMR (400 MHz, CDCl<sub>3</sub>): 1.45 (3H, d, *J* = 6 Hz, NCHCH<sub>3</sub>); 3.65 and 3.75 (2H, dd, *J* = 12 HzCH<sub>2</sub>N); 4.65 (1H, q, *J* = 6 Hz; NCHMe); 7.30-7.40 (4H, m, aryl-H); 7.40-7.5 (3H, m, aryl-H); 7.6-7.7 (3H, m, aryl-H); 7.8-7.85 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H); 8.55 (1H, d, *J* = 3 Hz, aryl-H); 8.65 (1H, bs, aryl-H).

15

**Example 23**

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(benzimidazol-2-yl)methyl)amine



Step 1) 4-Methoxy-3-(benzimidazol-2-yl)benzenecarboxaldehyde

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Pd(Ph<sub>3</sub>)<sub>4</sub> (72 mg, 0.062 mmol) was added to a degassed solution of 2-chlorobenzimidazole (0.95 g, 6.25 mmol) in 1,2-dimethoxyethane (25 mL), followed by 2M Na<sub>2</sub>CO<sub>3</sub> (15 mL) and 5-formyl-2-methoxybenzeneboronic acid (1.35 g, 7.5 mmol). The mixture was stirred at 115 C for 16 hours then more catalyst was added (2% mol) and reaction stirred for further 4 hours. The mixture was cooled and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure and the residue purified by column chromatography (1/1 hexane/ethyl acetate) to afford 0.285 g of title compound. C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> Mass (calculated): [252]; (found) [M+H<sup>+</sup>] = 253 NMR (400 MHz, CDCl<sub>3</sub>): 4.1 (3H, s, CH<sub>3</sub>O); 7.2 (1H, d, *J* = 8 Hz, aryl-H); 7.3-7.35 (2H, m, aryl-H); 7.5 (1H, m, aryl-H); 7.8 (1H, m, aryl-H); 8 (1H, dd, *J* = 2 and 8 Hz, aryl-H); 9 (1H, d, *J* = 1 Hz, aryl-H); 10 (1H, s, CHO); 10.4 (1H, bd, NH).

Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(benzimidazol-2-yl)lmethyl)amine

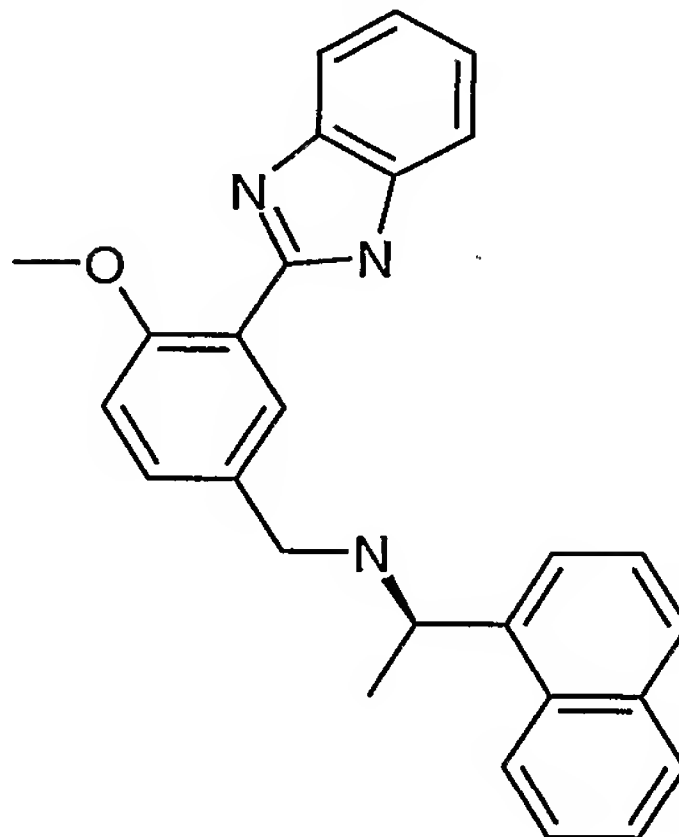
The title compound was prepared from 4-methoxy-3-(benzimidazol-2-yl)benzenecarboxaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O Mass (calculated): [357]; (found): [M+H<sup>+</sup>] = 358, 715 NMR (400 MHz, CDCl<sub>3</sub>): 1.3 (3H, d, *J* = 6 Hz, NCHCH<sub>3</sub>); 3.55 and 3.65 (2H, dd, *J* = 12 Hz, CH<sub>2</sub>N); 3.75 (1H, q, *J* = 6 Hz; NCHMe); 4.0 (3H, s, CH<sub>3</sub>O); 6.95 (1H, d, *J* = 8 Hz, aryl-H); 7.15-7.25 (3H, m, aryl-H); 7.25-7.35 (5H, m, aryl-H); 7.45 (1H, bd, aryl-H); 7.75 (1H, bd, aryl-H); 8.3 (1H, d, *J* = 1 Hz, aryl-H).

25

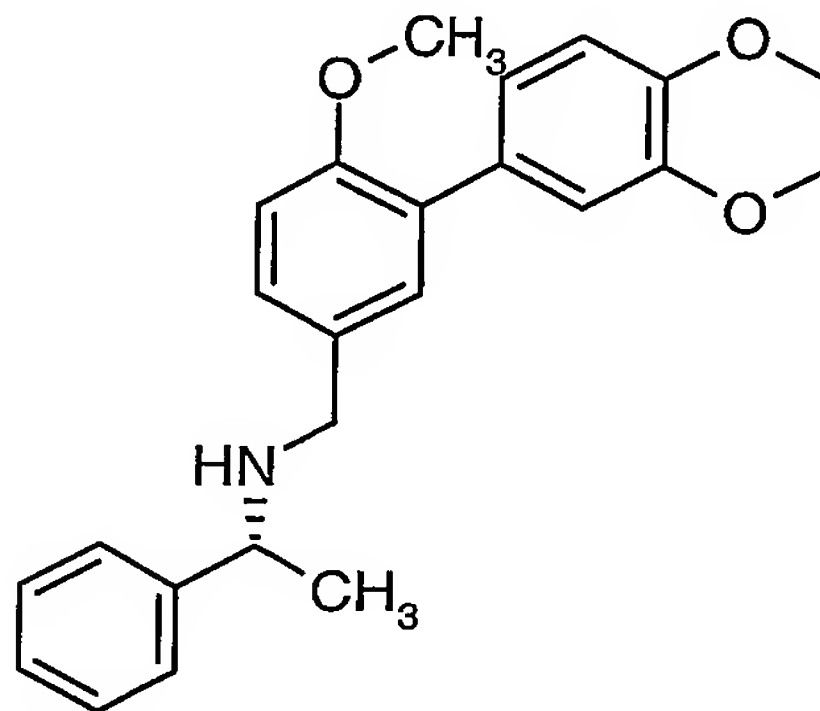
30

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**Example 24****(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(benzimidazol-2-yl)lmethyl)amine**

The title compound was prepared from 4-methoxy-3-(benzimidazol-2-yl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{27}H_{25}N_3O$  Mass (calculated): [407]; (found):  $[M+H^+] = 408$  NMR (400 MHz,  $CDCl_3$ ): 1.5 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.75 and 3.8 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 4.1 (3H, s,  $CH_3O$ ); 4.75 (1H, q,  $J = 6$  Hz;  $NCHMe$ ); 7.0 (1H, d,  $J = 8$  Hz, aryl-H); 7.25-7.3 (2H, m, aryl-H); 7.45-7.55 (4H, m, aryl-H); 7.75-7.9 (4H, m, aryl-H); 8.2 (1H, d,  $J = 8$  Hz, aryl-H); 8.55 (1H, d,  $J = 1$  Hz, aryl-H).

**Example 25****(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(1,4-benzodioxan-5-yl)lmethyl)amine**

Step 1) 4-methoxy-3-(1,4-benzodioxan-5-yl)benzenecarboxaldehyde

- 53 -

A solution of 5-formyl-2-methoxybenzeneboronic acid (1 g, 5.6 mmol), 3,4-ethylenedioxybromobenzole (1 g, 4.65 mmol) and  $K_2CO_3$  (1.6 g, 11.6 mmol) in ethanol (20 mL) and toluene (40 mL) was degassed prior to addition of  $Pd(Ph_3)_4$  (54 mg, 0.046 mmol). The mixture was refluxed for 24 hours then cooled and  
5 filtered through diatomaceous earth. The filtrate was concentrated in vacuo, extracted with ethyl acetate, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (heptane/ethyl acetate 7/3) to give 1 g of title compound.  $C_{16}H_{14}O_4$  Mass (calculated): [270]; (found):  $[M+H^+] = 271, 312$   
10 NMR (400 MHz,  $CDCl_3$ ): 3.95 (3H, s,  $CH_3O$ ); 4.3 (4H, s,  $OCH_2CH_2O$ ); 6.9-7.15 (4H, m, aryl-H); 7.9-7.95 (2H, m, aryl-H); 10 (1H, s, CHO).

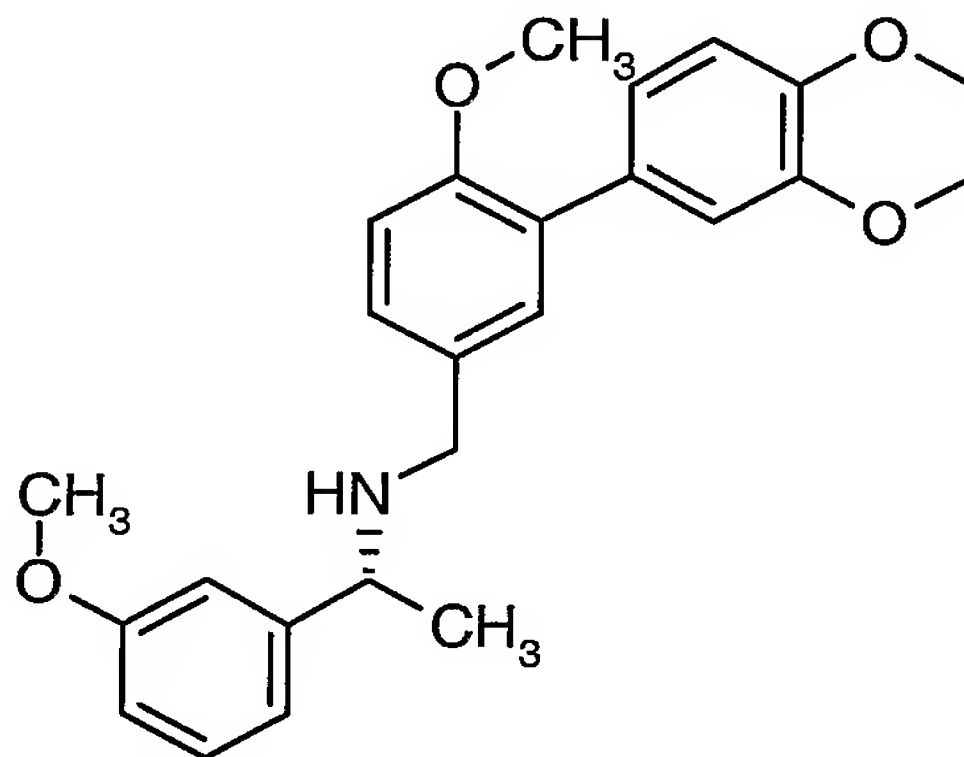
Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(1,4-benzodioxan-5-yl)methyl)amine

15 The title compound was prepared from 4-methoxy-3-(1,4-benzodioxan-5-yl)benzenecarboxaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.  
 $C_{24}H_{25}NO_3$  Mass (calculated): [375]; (found):  $[M+H^+] = 376, 255$  NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7 (3H, s,  $CH_3O$ ); 3.75 (1H, q,  $J = 6$  Hz;  $NCHMe$ ); 4.2 (4H, s,  $OCH_2CH_2O$ ); 6.8 (2H, m, aryl-H); 6.95 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.05 (1H, d,  $J = 1$  Hz, aryl-H); 7.15-7.3 (3H, m, aryl-H); 7.35-7.45 (4H, m, aryl-H).  
20

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**Example 26**

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(1,4-benzodioxan-5-yl)methyl)amine



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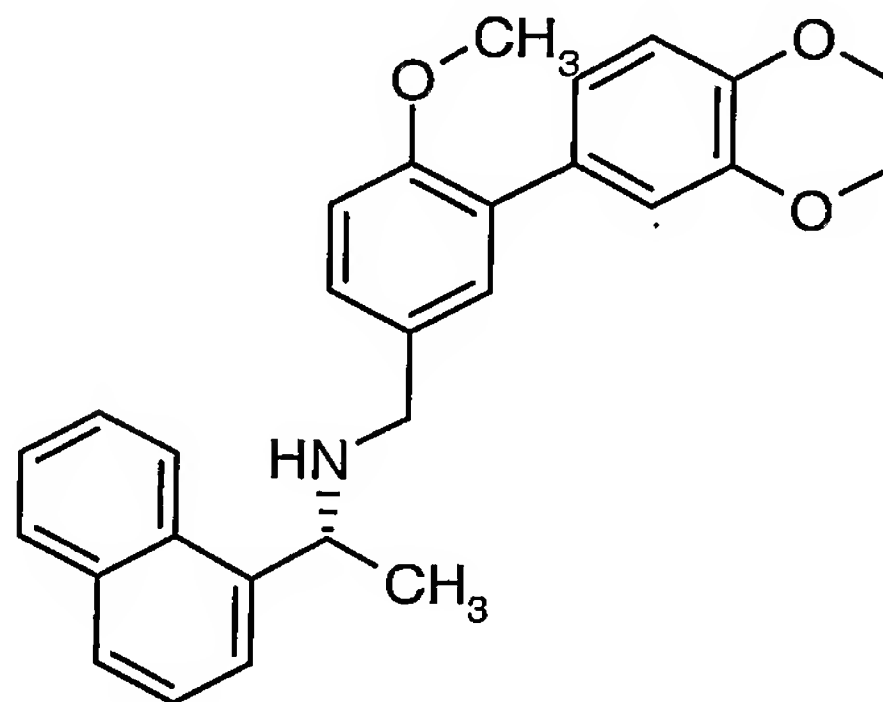
The title compound was prepared from 4-methoxy-3-(1,4-benzodioxan-5-yl)benzenecarboxaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

10  $C_{25}H_{27}NO_4$  Mass (calculated): [405]; (found):  $[M+H^+] = 406$ , 255 NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.75 (3H, s,  $CH_3O$ ); 3.77 (3H, s,  $CH_3O$ ); 3.75 (1H, m;  $NCHMe$ ); 4.2 (4H, s,  $OCH_2CH_2O$ ); 6.7 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.8-6.9 (4H, m, aryl-H); 7.0 (1H, dd, dd,  $J = 1$  and 8 Hz, aryl-H); 7.1 (1H, d,  $J = 1$  Hz, aryl-H); 7.25-7.3 (3H, m, aryl-H).

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**Example 27**

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(1,4-benzodioxan-5-yl)-methyl)amine



5

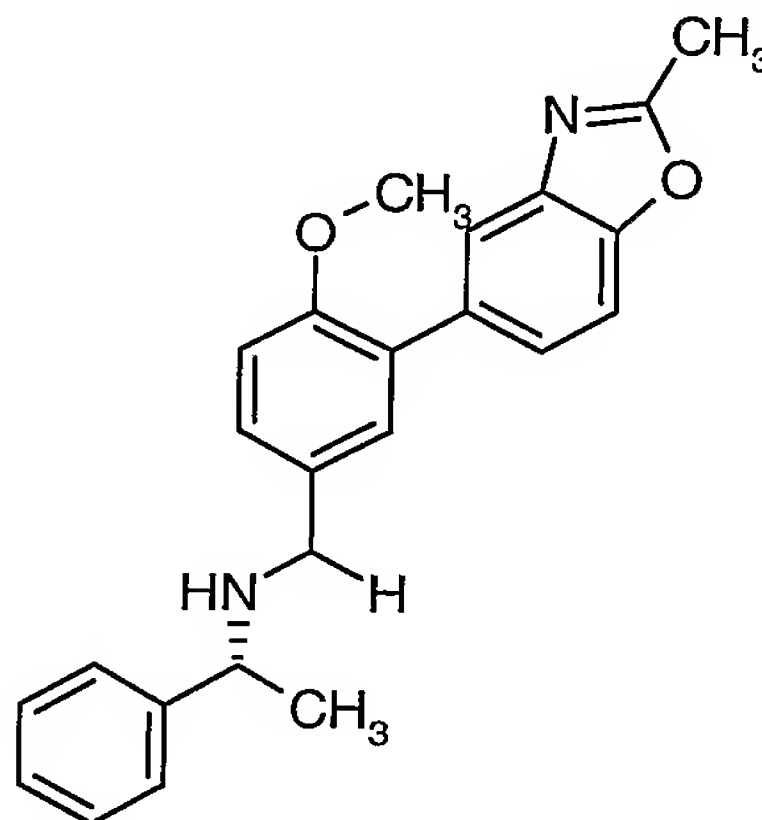
The title compound was prepared from 4-methoxy-3-(1,4-benzodioxan-5-yl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

10  $C_{28}H_{28}NO_3$  Mass (calculated): [425]; (found):  $[M+H^+] = 426, 255$ . NMR (400 MHz,  $CDCl_3$ ): 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7 (3H, s,  $CH_3O$ ); 4.2 (4H, s,  $OCH_2CH_2O$ ); 4.65 (1H, q,  $J = 6$  Hz;  $NCHMe$ ); 6.8 (2H, m, aryl-H); 6.9 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.0 (1H, d,  $J = 1$  Hz, aryl-H); 7.1-7.15 (2H, m, aryl-H); 7.35-7.45 (3H, m, aryl-H); 7.7 (2H, d,  $J = 8$  Hz, aryl-H); 7.8 (1H, m, aryl-H); 8.0 (1H, m, aryl-H).

15



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**Example 28****(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2-methylbenzoxazol-5-yl)methyl)amine**Step 1) 2-Amino-4-bromophenol:

- 5 A solution of 4-bromo-2-nitrophenol (2 g, 9.17 mmol) and tin (II) chloride (10.35 g, 45.9 mmol) in ethanol (20 mL) was heated at 70°C for 2 hours, then cooled, poured onto ice, neutralized with NaHCO<sub>3</sub>. The aqueous phase was then extracted with ethyl acetate, dried over sodium sulphate and the solvent removed in vacuo to afford 1.61 g of the title compound. C<sub>6</sub>H<sub>6</sub>BrNO Mass (calculated): [188];
- 10 (found): [M+H<sup>+</sup>] = 188, 190 (Br) NMR (400 MHz, dmso-d<sub>6</sub>): 4.8 (2H, bs, NH<sub>2</sub>); 6.5 (1H, dd, *J* = 2 and 8 Hz, aryl-H); 6.6 (1H, d, *J* = 8 Hz, aryl-H); 6.75 (1H, d, *J* = 2 Hz, aryl-H); 9.3 (1H, bs, OH).

Step 2) 2-methyl-5-bromobenzoxazole:

- 15 A solution of 2-amino-4-bromophenol (1 g, 5.32 mmol) in trimethyl orthoacetate (20 mL) was refluxed for 1.5 hours. The reaction was then cooled and the solvent removed under reduced pressure to give 1.1 g of title compound.

C<sub>8</sub>H<sub>6</sub>BrNOMass (calculated): [212]; (found): [M+H<sup>+</sup>] = 212, 214 (Br).

- 20 NMR (400 MHz, dmso-d<sub>6</sub>): 2.55 (3H, s, CH<sub>3</sub>); 7.3 (1H, d, *J* = 8 Hz, aryl-H); 7.35 (1H, dd, *J* = 1 and 8 Hz, aryl-H); 7.75 (1H, d, *J* = 2 Hz, aryl-H).

Step 3) 4-methoxy-3-(2-methylbenzoxazol-5-yl)benzenecarboxaldehyde

A solution of 5-formyl-2-methoxybenzeneboronic acid (1 g, 5.6 mmol), 2-methyl-5-bromobenzoxazole (1 g, 4.72 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.63 g, 11.8 mmol) in

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ethanol (20 mL) and toluene (40 mL) was degassed prior to addition of  $\text{Pd}(\text{Ph}_3)_4$  (55 mg, 0.047 mmol). The mixture was refluxed for 20 hours then cooled and filtered through diatomaceous earth. The filtrate was concentrated in vacuo, extracted with ethyl acetate, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (heptane/ethyl acetate 7/3 to 6/4) to give 1.13 g of title compound.



Mass (calculated): [267]; (found):  $[\text{M}+\text{H}^+]$ : 268.

NMR (400 MHz,  $\text{CDCl}_3$ ): 2.6 (3H, s,  $\text{CH}_3$ ); 3.85 (3H, s,  $\text{CH}_3\text{O}$ ); 7.05 (1H, d,  $J = 8$  Hz, aryl-H); 7.35 (1H, d,  $J = 8$  Hz, aryl-H); 7.45 (1H, d,  $J = 8$  Hz, aryl-H); 7.75 (1H, s, aryl-H); 7.8-7.85 (2H, m, aryl-H); 9.9 (1H, s, CHO).

Step 4) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2-methylbenzoxazol-5-yl)methyl)amine:

The title compound was prepared from 4-methoxy-3-(benzimidazol-2-yl)benzenecarboxaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

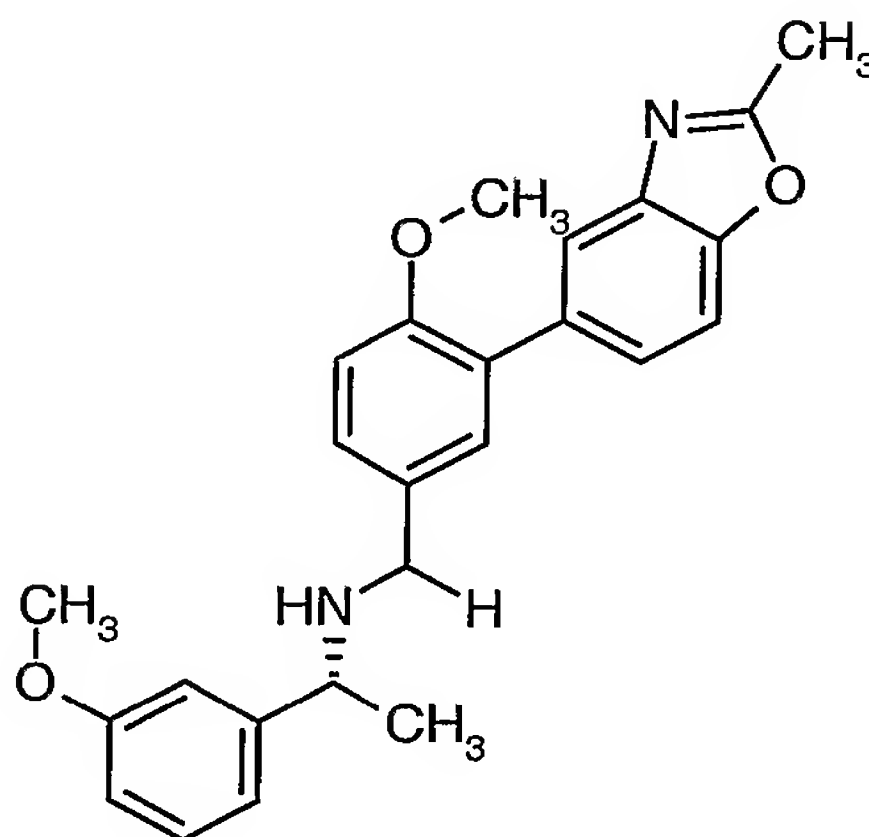


Mass (calculated): [372]; (found):  $[\text{M}+\text{H}^+] = 373$ .

NMR (400 MHz,  $\text{CDCl}_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $\text{NCHCH}_3$ ); 2.6 (3H, s,  $\text{CH}_3$ ); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz,  $\text{CH}_2\text{N}$ ); 3.7 (3H, s,  $\text{CH}_3\text{O}$ ); 3.75 (1H, q,  $J = 6$  Hz;  $\text{NCHMe}$ ); 6.8 (1H, d,  $J = 8$  Hz, aryl-H); 7.2-7.3 (3H, m, aryl-H); 7.3-7.35 (4H, m, aryl-H); 7.4 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.45 (1H, d,  $J = 8$  Hz, aryl-H); 7.7 (1H, d,  $J = 1$  Hz, aryl-H).

**Example 29**

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(2-methylbenzoxazol-5-yl)methyl)amine



5

The title compound was prepared from 4-methoxy-3-(2-methylbenzoxazol-5-yl)benzenecarboxyaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

$C_{25}H_{26}N_2O_3$

10 Mass (calculated): [402]; (found):  $[M+H^+] = 403$ .

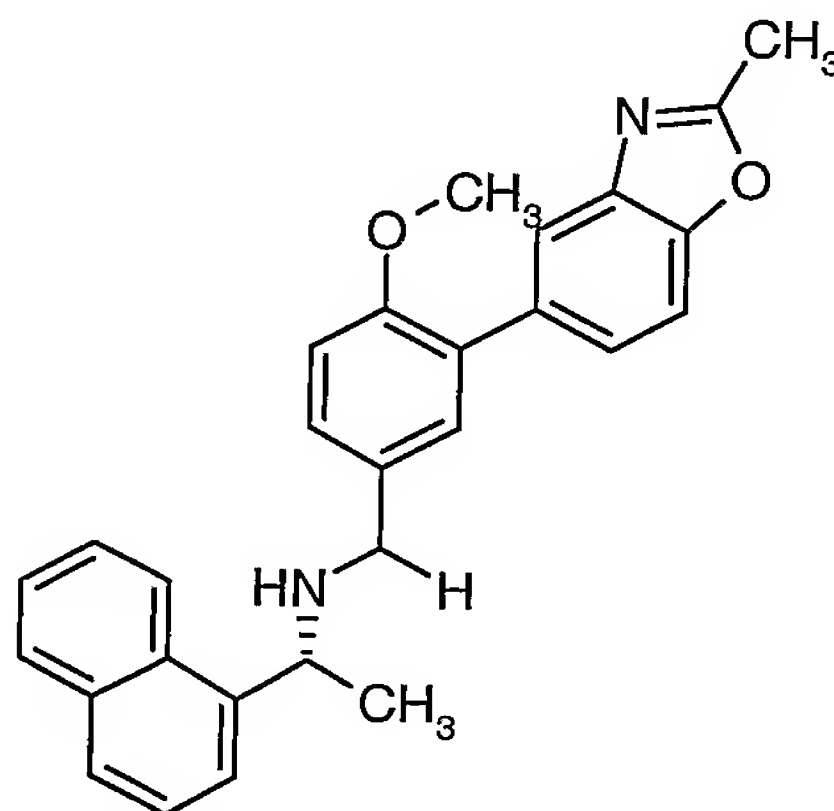
NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, bd,  $J = 6$  Hz,  $NCHCH_3$ ); 2.6 (3H, s,  $CH_3$ ); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7 (3H, s,  $CH_3O$ ); 3.72 (3H, s,  $CH_3O$ ); 3.75 (1H, q,  $J = 6$  Hz;  $NCHMe$ ); 6.75 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.8-6.9 (3H, m, aryl-H); 7.2-7.3 (3H, m, aryl-H); 7.4 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.45 (1H, d,  $J = 8$  Hz, aryl-H); 7.7 (1H, d,  $J = 1$  Hz, aryl-H).

15

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**Example 30**

(R)-N-(1-(1-Naphthylethyl)-N-((4-methoxy-3-(2-methylbenzoxazol-5-yl)methyl)amine



5

The title compound was prepared from 4-methoxy-3-(2-methylbenzoxazol-5-yl)benzenecarboxyaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

 $C_{28}H_{26}N_2O_2$ 

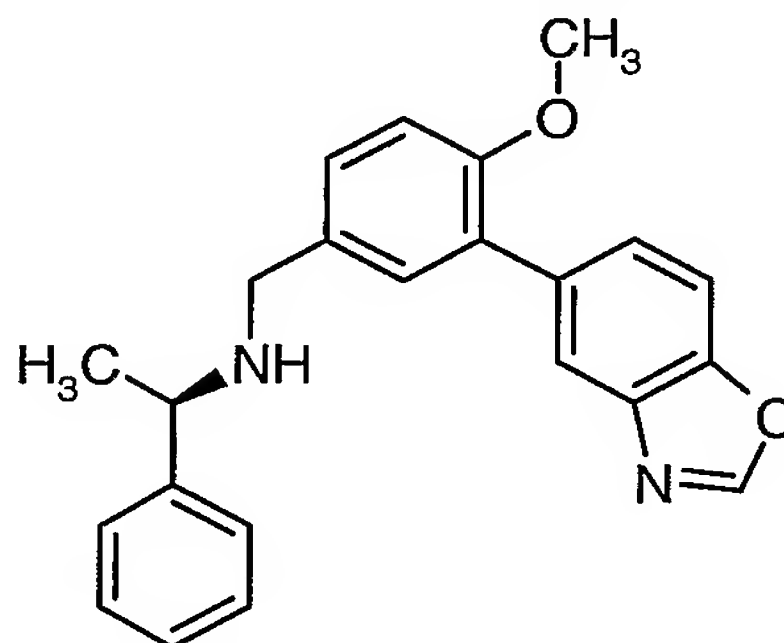
10

Mass (calculated): [422]; (found):  $[M+H^+] = 423$ .

NMR (400 MHz,  $CDCl_3$ ): 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 2.6 (3H, s,  $CH_3$ ); 3.6 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7 (3H, s,  $CH_3O$ ); 4.6 (1H, q,  $J = 6$  Hz;  $NCHMe$ ); 6.8 (1H, d,  $J = 8$  Hz, aryl-H); 7.2-7.3 (3H, m, aryl-H); 7.35 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.4-7.5 (3H, m, aryl-H); 7.7-7.75 (3H, m, aryl-H); 7.8-7.85 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

15

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**Example 31****(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(benzoxazol-5-yl)methyl)amine**Step 1) 5-Bromobenzoxazole:

- 5 A solution of 2-amino-4-bromophenol (2 g, 10.6 mmol) in triethylorthoformate (40 mL) was refluxed for 1.5 hours. The reaction was then cooled and the solvent removed under reduced pressure to give a crude which was purified by washing through a plug of silica eluting with hexane/ethyl acetate 3/2 to afford 1.1 g of title compound.  $C_7H_4BrNO$  Mass (calculated): [198]; (found):  $[M+H^+] = 198, 200$
- 10 (Br) NMR (400 MHz,  $CDCl_3$ ): 7.25-7.3 (2H, m, aryl-H); 7.8 (1H, d,  $J = 1$ , aryl-H); 8.0 (1H, s, aryl-H).

Step 2) 4-Methoxy-3-(benzoxazol-5-yl)benzenecarboxyaldehyde:

- A solution of 5-formyl-2-methoxybenzeneboronic acid (1 g, 5.6 mmol), 2-methyl-5-bromobenzoxazole (1 g, 4.72 mmol) and  $K_2CO_3$  (1.63 g, 11.8 mmol) in ethanol (20 mL) and toluene (40 mL) was degassed prior to addition of  $Pd(Ph_3)_4$  (55 mg, 0.047 mmol). The mixture was refluxed for 20 hours then cooled and filtered through diatomaceous earth. The filtrate was concentrated in vacuo, extracted with ethyl acetate, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (heptane/ethyl acetate 7/3 to 6/4) to give 1.13 g of title compound.
- 20  $C_{15}H_{11}NO_3$
- Mass (calculated): [253]; (found):  $[M+H^+]$ : 254, 295.
- NMR (400 MHz,  $CDCl_3$ ): 2.6 (3H, s,  $CH_3$ ); 3.95 (3H, s,  $CH_3O$ ); 7.15 (1H, d,  $J = 8$  Hz, aryl-H); 7.55 (1H, d,  $J = 8$  Hz, aryl-H); 7.65 (1H, d,  $J = 8$  Hz, aryl-H); 7.85-7.95 (2H, aryl-H); 8 (1H, s, aryl-H); 8.15 (1H, s, aryl-H); 10.0 (1H, s, CHO).
- 25

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Step 3) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(benzoxazol-5-yl)methyl)amine:

The title compound was prepared from 4-methoxy-3-(benzoxazol-5-yl)benzenecarboxyaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

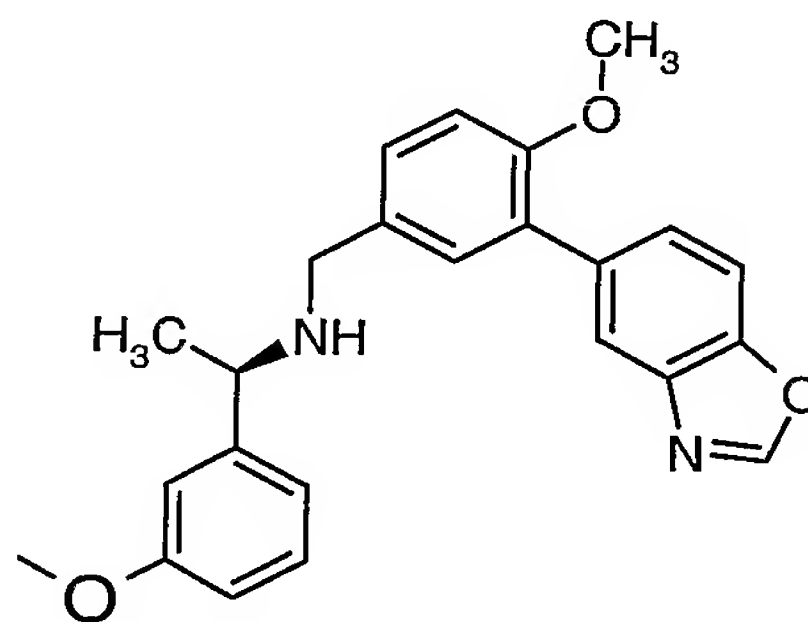


Mass (calculated): [358]; (found):  $[\text{M}+\text{H}^+] = 359, 831$ .

NMR (400 MHz,  $\text{CDCl}_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $\text{NCHCH}_3$ ); 2.6 (3H, s,  $\text{CH}_3$ ); 3.5 and 3.55 (2H, dd,  $J = 12$  Hz,  $\text{CH}_2\text{N}$ ); 3.7 (3H, s,  $\text{CH}_3\text{O}$ ); 3.75 (1H, q,  $J = 6$  Hz;  $\text{NCHMe}$ ); 6.85 (1H, d,  $J = 8$  Hz, aryl-H); 7.1-7.2 (3H, m, aryl-H); 7.2-7.3 (4H, m, aryl-H); 7.45 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.5 (1H, d,  $J = 8$  Hz, aryl-H); 7.8 (1H, d,  $J = 1$  Hz, aryl-H); 8 (1H, s, aryl-H).

**Example 32**

(R)-N-(1-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(benzoxazol-5-yl)methyl)amine



The title compound was prepared from 4-methoxy-3-(benzoxazol-5-yl)benzenecarboxyaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.



Mass (calculated): [388]; (found):  $[\text{M}+\text{H}^+] = 389, 891$ .

NMR (400 MHz,  $\text{CDCl}_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $\text{NCHCH}_3$ ); 2.6 (3H, s,  $\text{CH}_3$ ); 3.5 and 3.55 (2H, dd,  $J = 12$  Hz,  $\text{CH}_2\text{N}$ ); 3.7-3.8 (4H, m,  $\text{CH}_3\text{O}$  and  $\text{NCHMe}$ ); 6.7 (1H, dd,  $J = 2$  and 8 Hz, aryl-H); 6.8-6.9 (3H, m, aryl-H); 7.15-7.25 (3H, m, aryl-H);

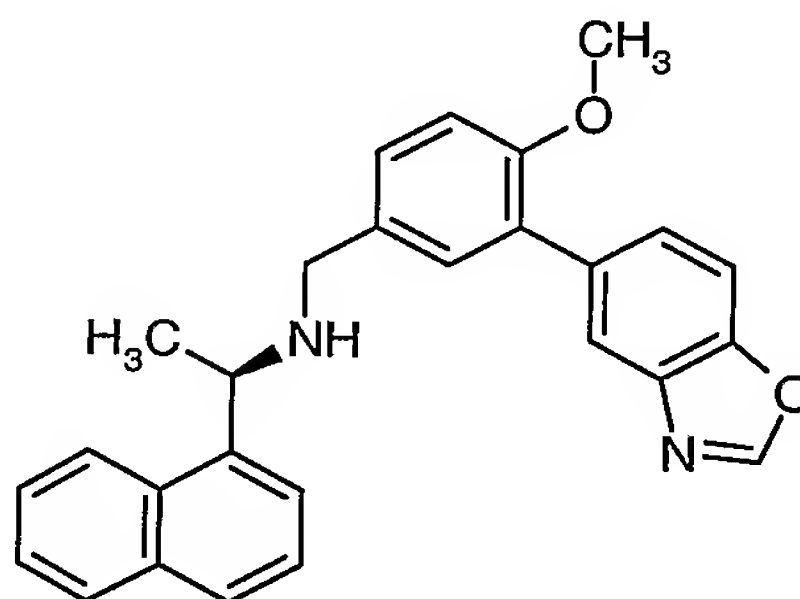


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H); 7.45 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.5 (1H, d,  $J = 8$  Hz, aryl-H); 7.85 (1H, d,  $J = 1$  Hz, aryl-H); 8 (1H, s, aryl-H).

**Example 33**

5 (R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(benzoxazol-5-yl)methyl)amine



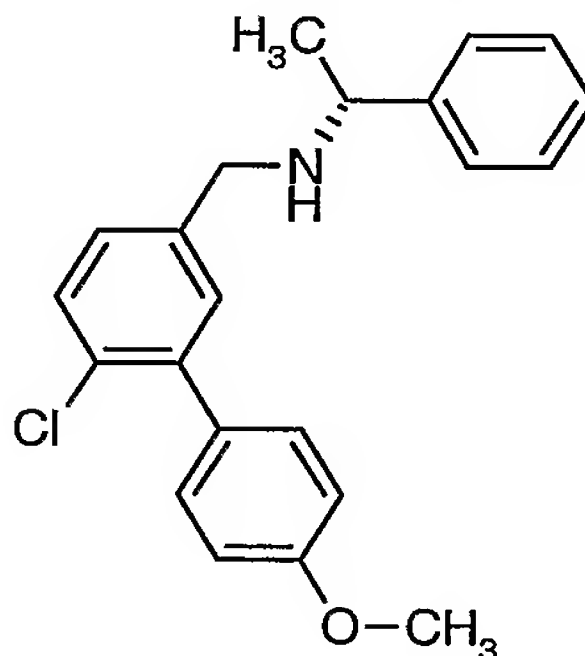
The title compound was prepared from 4-methoxy-3-(benzoxazol-5-yl)benzene-carboxyaldehyde and (R)-1-(1-naphthyl)ethylamine according to general  
10 procedure C.

$C_{27}H_{24}N_2O_2$

Mass (calculated): [408]; (found):  $[M+H^+] = 409, 931$ .

NMR (400 MHz,  $CDCl_3$ ): 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7 (3H, s,  $CH_3O$ ); 4.65 (1H, q,  $J = 6$  Hz;  $NCHMe$ ); 6.85 (1H, d,  $J = 8$  Hz, aryl-H); 7.2-7.3 (2H, m, aryl-H); 7.4-7.5 (4H, m, aryl-H); 7.5 (1H, d,  $J = 6$  Hz, aryl-H); 7.7-7.75 (2H, m, aryl-H); 7.75-7.8 (1H, m, aryl-H); 7.85 (1H, d,  $J = 1$  Hz, aryl-H); 8 (1H, s, aryl-H); 8.05-8.1 (1H, m, aryl-H).

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**Example 34****(R)-N-(1-Phenylethyl)-N-((4-chloro-3-(4'-methoxyphenyl)phenyl)methyl)amine****5    Step 1) 3-Bromo-4-chlorobenzyl alcohol:**

A solution of 3-bromo-4-chlorobenzoic acid (3.53 g, 15 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0 C prior to addition of borane (1M soln in THF, 20 mL, 20 mmol). The solution was then heated at 65 C for 12 hours then cooled to 0 C and methanol was added dropwise to quench excess borane. The solvent was evaporated under reduced pressure, the residue was redissolved in ethyl acetate and washed with saturated NH<sub>4</sub>Cl then brine, dried over sodium sulphate. The solvent was removed in vacuo to afford 3.23 g of title compound.

**C<sub>7</sub>H<sub>6</sub>BrClO**Mass (calculated): [221], MH<sup>+</sup> not found.

15    NMR (400 MHz, CDCl<sub>3</sub>): 4.6 (2H, s, CH<sub>2</sub>OH); 7.15 (1H, dd, *J* = 1 and 8 Hz, aryl-H); 7.35 (1H, d, *J* = 8 Hz, aryl-H); 7.55 (1H, d, *J* = 1 Hz, aryl-H).

**Step 2) 3-Bromo-4-chlorobenzaldehyde:**

20    A solution of 3-bromo-4-chlorobenzyl alcohol (3.24 g, 14.6 mmol) in acetone (100 mL) was treated with MnO<sub>2</sub> (16.2 g, 73 mmol) and the mixture stirred for 3 days then filtered over diatomaceous earth. The filtrate was concentrated under reduced pressure to afford 2.0 g of title compound.

**C<sub>7</sub>H<sub>4</sub>BrClO**Mass (calculated): [219]; MH<sup>+</sup> not found.

25    NMR (400 MHz, CDCl<sub>3</sub>): 7.55 (1H, d, *J* = 8 Hz, aryl-H); 7.7 (1H, dd, *J* = 1 and 8 Hz, aryl-H); ; 8.05 (1H, d, *J* = 1 Hz, aryl-H); 9.85 (1H, s, CHO).

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Step 3) 4-chloro-3-(4-methoxyphenyl)benzenecarboxaldehyde:

To a degassed solution of 4-methoxybenzeneboronic acid (1.51 g, 10 mmol), 3-bromo-4-chlorobenzaldehyde (2 g, 9.13 mmol), and potassium carbonate (3.13 g, 22.8 mmol) in toluene/ethanol 2/1, (60 mL), Pd(PPh<sub>3</sub>)<sub>4</sub> (130 mg, 1mol%) is added  
5 and the mixture is degassed for further 5 minutes. The mixture is then refluxed for 2 days. The mixture was partitioned between ethyl acetate and water and extracted. The organic solvent was dried over sodium sulphate, removed under reduced pressure, and the residue purified by column chromatography (heptane/ethyl acetate 19/1 to afford 1.41 g of product.

10 C<sub>14</sub>H<sub>11</sub>ClO<sub>2</sub>Mass (calculated): [246]; MH<sup>+</sup> not found.

NMR (400 MHz, CDCl<sub>3</sub>): 3.8 (3H, s, MeO); 6.9 (2H, d, *J* = 8 Hz, aryl-H); 7.35 (2H, d, *J* = 8 Hz, aryl-H); 7.55 (1H, d, *J* = 8 Hz, aryl-H); 7.7 (1H, dd, *J* = 2 and 8 Hz, aryl-H); 7.75 (1H, d, *J* = 2 Hz, aryl-H); 9.9 (1H, s, CHO).

15

Step 4) (R)-N-(1-Phenylethyl)-N-((4-chloro-3-(4'-methoxyphenyl)phenyl)methyl)amine:

The title compound was prepared from 4-chloro-3-(4-methoxyphenyl)-benzenecarboxaldehyde and (R)-α-methylbenzylamine according to general  
20 procedure C.

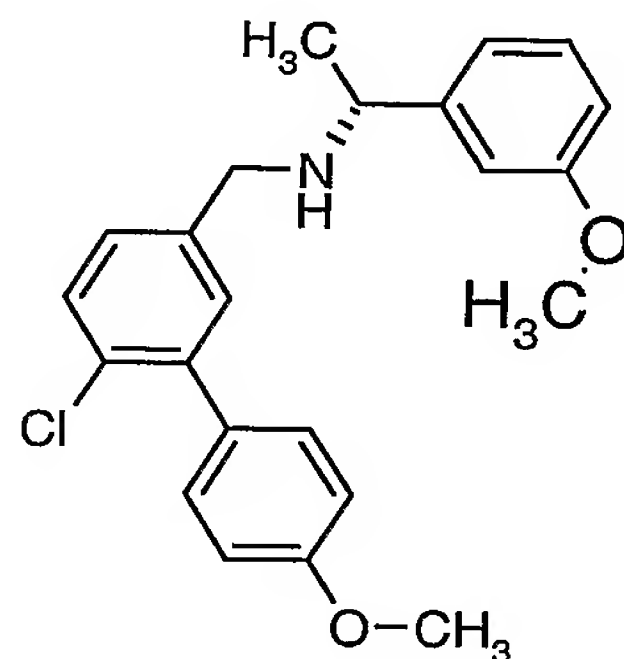
C<sub>22</sub>H<sub>22</sub>ClNOMass (calculated): [351]; (found): [M+H<sup>+</sup>] = 352, 354 (Cl).

NMR (400 MHz, CDCl<sub>3</sub>): 1.15 (3H, d, *J* = 6 Hz, NCHCH<sub>3</sub>); 3.4 and 3.45 (2H, dd, *J*=12 Hz, CH<sub>2</sub>N); 3.55 (1H, m, NCHMe); 3.6 (3H, s, MeO); 6.8 (2H, d, *J* = 8 Hz, aryl-H); 7 (1H, dd, *J* = 1 and 8 Hz, aryl-H); 7.05-7.1 (2H, m, aryl-H); 7.15-7.25  
25 (7H, m, aryl-H).

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**Example 35**

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-chloro-3-(4'-methoxyphenyl)-phenylmethyl)amine



5

The title compound was prepared from 4-chloro-3-(4-methoxyphenyl)benzene-carboxaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

$C_{23}H_{23}ClNO_2$

10 Mass (calculated): [381]; (found):  $[M+H^+] = 382, 384$  (Cl).

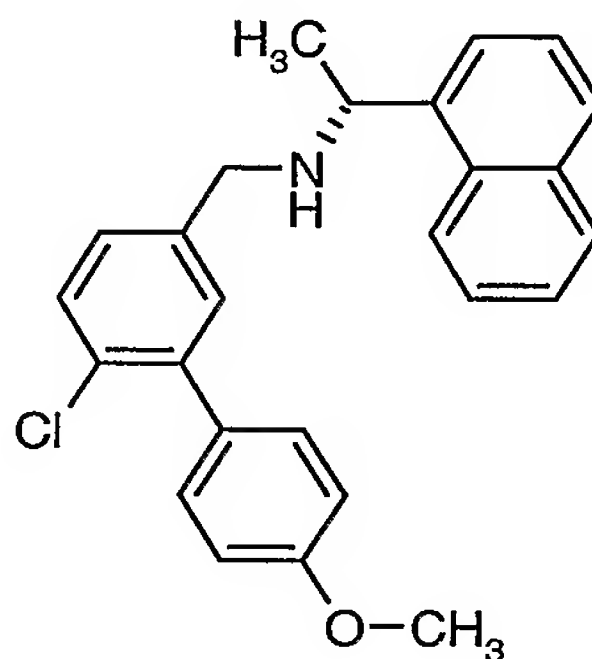
NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7-3.75 (4H, m,  $NCHMe$  and  $MeO$ ); 3.8 (3H, s,  $MeO$ ); 6.75 (1H, dd,  $J = 2$  and 8 Hz, aryl-H); 7.85 (1H, d,  $J = 1$  Hz, aryl-H); 7.9 (2H, d,  $J = 8$  Hz, aryl-H); 7.15 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.15-7.25 (2H, m, aryl-H); 7.3-7.4 (3H, m, aryl-H).

15

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**Example 36**

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-chloro-3-(4'-methoxyphenyl)phenyl)methyl)amine



5

The title compound was prepared from 4-chloro-3-(4-methoxyphenyl)benzene-carboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{26}H_{24}ClNO$

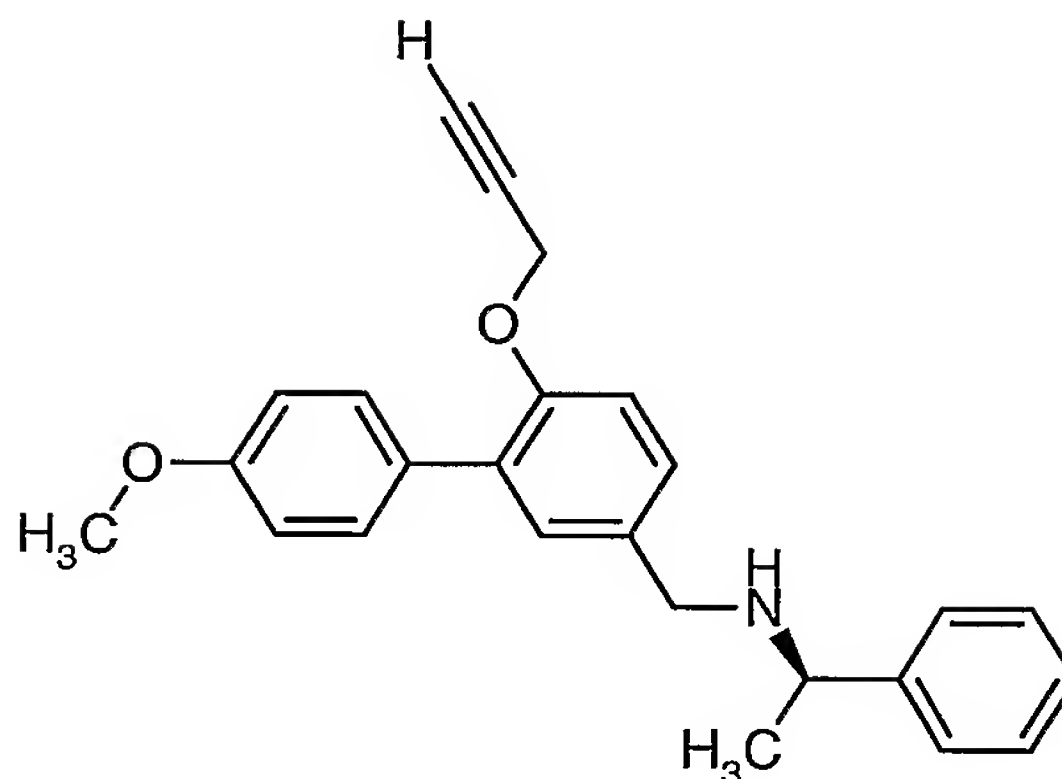
- 10 Mass (calculated): [401]; (found):  $[M+H^+] = 402, 404$  (Cl).  
 NMR (400 MHz,  $CDCl_3$ ): 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 and 3.65 (2H, dd,  $J=12$  Hz,  $CH_2N$ ); 3.75 (3H, s, MeO); 4.6 (1H, m,  $NCHMe$ ); 6.85 (2H, d,  $J = 8$  Hz, aryl-H); 7.1 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.2 (1H, d,  $J = 1$  Hz, aryl-H); 7.3-7.35 (3H, m, aryl-H); 7.4-7.45 (3H, m, aryl-H); 7.65-7.7 (2H, m, aryl-H); 7.8-  
 15 7.85 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

**Example 37**

(R)-N-(1-Phenylethyl)-N-((4-propargyloxy-3-(4'-methoxyphenyl)phenyl)methyl)amine

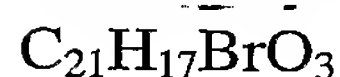
20

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Step 1) Benzyl 4-benzyloxy-3-bromobenzoate:

A 500mL round bottom flask was charged with DMF (250 mL), 3-bromo-4-hydroxybenzoic acid (8.68 g, 40 mmol), potassium carbonate (22.06 g, 160 mmol), potassium iodide (50 mg) and benzyl bromide (9.26 mL, 78 mmol). The mixture was heated at 75 C for 3 days, then cooled, the solvent removed under reduced pressure and the residue redissolved in ethyl acetate and washed with aqueous potassium carbonate, then brine. The organic layer was dried over sodium sulphate then removed under reduced pressure to give an off-white solid which was purified by column chromatography (eluting with DCM/hexane 1/1) to give 12.1 g of title compound).



Mass (calculated): [397]; found 397, 399 (Br).

NMR (400 MHz,  $\text{CDCl}_3$ ): 5.15 (2H, s,  $\text{OCH}_2\text{Ph}$ ); 5.25 (2H, s,  $\text{OCH}_2\text{Ph}$ ); 6.85 (1H, d,  $J = 8$  Hz, aryl-H); 7.3-7.5 (10H, m, aryl-H); 7.9 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 8.2 (1H, d,  $J = 1$  Hz, aryl-H).

Step 2) Benzyl 4-benzyloxy-3-(4-methoxyphenyl)benzoate:

To a degassed solution of 4-methoxybenzeneboronic acid (5.0 g, 32.9 mmol), benzyl 4-benzyloxy-3-bromobenzoate (12.1 g, 30.5 mmol), and potassium carbonate (10.4 g, 76.2 mmol) in toluene/ethanol 2/1, (140 mL),  $\text{Pd}(\text{PPh}_3)_4$  (400 mg, 1mol%) was added and the mixture is degassed for further 5 minutes. The mixture is then refluxed for 12 hours. The mixture was partitioned between ethyl acetate and water and extracted. The organic solvent was dried over sodium sulphate, removed under reduced pressure, and the residue purified by column



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chromatography (9/1 DCM/hexane) to afford 0.73 g of pure title compound, 9.74 g of a 4:6 mixture of title compound and the corresponding ethyl ester, and 0.71 g of the ethyl ester derivative.



5 NMR (400 MHz,  $\text{CDCl}_3$ ):  $\text{C}_{28}\text{H}_{24}\text{O}_4$

Ethyl ester: NMR (400 MHz,  $\text{CDCl}_3$ ): 1.3 (3H, t,  $J = 6$  Hz,  $\text{OCH}_2\text{CH}_3$ ); 3.75 (3H, s,  $\text{CH}_3\text{O}$ ); 4.3 (2H, q,  $J = 6$  Hz,  $\text{OCH}_2\text{CH}_3$ ); 5.1 (2H, s,  $\text{OCH}_2\text{Ph}$ ); 6.95 (2H, m, aryl-H); 7.2-7.3 (2H, m, aryl-H); 7.45 (2H, m, aryl-H); 7.85 (1H, dd,  $J = 1$  and 8 Hz, aryl-H).

10 Benzyl ester: NMR (400 MHz,  $\text{CDCl}_3$ ): 3.75 (3H, s,  $\text{CH}_3\text{O}$ ); 4.65 (2H, s,  $\text{OCH}_2\text{Ph}$ ); 5.1 (2H, s,  $\text{OCH}_2\text{Ph}$ ); 7 (2H, m, aryl-H); 7.2-7.3 (2H, m, aryl-H); 7.45 (2H, m, aryl-H); 8.05 (1H, dd,  $J = 1$  and 8 Hz, aryl-H).

15 Step 3) Ethyl 4-hydroxy-3-(4-methoxyphenyl)benzoate and 4-hydroxy-3-(4-methoxyphenyl)benzoic acid:

A mixture of benzyl and ethyl 4-benzyloxy-3-(4-methoxyphenyl)benzoates (9.74 g, ca, 22.9 mmol) was hydrogenated in THF/ethanol (100 mL) under atmospheric pressure for 60 hours, then the catalyst removed by filtration and the solvent evaporated in vacuo to afford 6.62 g of a mixture of the title compounds.

20  $\text{C}_{12}\text{H}_{14}\text{O}_4$

Mass (calculated): [244]; found: 245.

NMR (400 MHz,  $\text{CDCl}_3$ ): 3.8 (3H, s,  $\text{CH}_3\text{O}$ ); 5.8 (1H, bs, OH); 6.95 (3H, m, aryl-H); 7.35 (2H, d,  $J = 8$  Hz, aryl-H); 7.9-8 (2H, m, aryl-H).



25 Mass (calculated): [272]; found: 273.

NMR (400 MHz,  $\text{CDCl}_3$ ): 1.3 (3H, t,  $J = 6$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ); 3.8 (3H, s,  $\text{CH}_3\text{O}$ ); 4.3 (2H, q,  $J = 6$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ); 5.75 (1H, s, OH); 6.9-7 (3H, m, aryl-H); 7.35 (2H, d,  $J = 8$  Hz, aryl-H); 7.9-7.95 (2H, m, aryl-H).

Step 4) 4-hydroxy-3-(4-methoxyphenyl)benzyl alcohol:

30 A solution of Ethyl 4-hydroxy-3-(4-methoxyphenyl)benzoate and 4-hydroxy-3-(4-methoxyphenyl)benzoic acid (5.3 g, 19.47 mmol) in anhydrous THF (100 mL) was cooled to 0°C and treated with  $\text{LiAlH}_4$  (2.95 g, 77.8 mmol); the mixture was

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then heated at 65 C for one hour then cooled and aqueous NaOH (5%, 19.4 mL) was added drop wise. The resulting precipitate was filtered off and the filtrate concentrated under reduced pressure to afford 5.54 g of crude product.



5 Mass (calculated): [230]; found: 213  $[\text{MH}^+ - \text{OH}]$ .

NMR (400 MHz,  $\text{CDCl}_3$ ): 3.8 (3H, s,  $\text{CH}_3\text{O}$ ); 4.55 (2H, s,  $\text{CH}_2$ ); 6.9 (1H, d,  $J = 8$  Hz, aryl-H); 6.9-7 (2H, m, aryl-H); 7.25-7.35 (2H, m, aryl-H); 7.4-7.45 (2H, m, aryl-H).

10 Step 5) 4-Hydroxy-3-(4-methoxyphenyl)benzaldehyde:

A solution of 4-hydroxy-3-(4-methoxyphenyl)benzyl alcohol (5.54 g, 24 mmol) in acetone (250 mL) was treated with  $\text{MnO}_2$  and the mixture stirred for 3 days. The solid was filtered on diatomaceous earth and the filtrate was concentrated under reduced pressure to afford 5.96 g of title compound as a pale green oil, impure with manganese salts.



Mass (calculated): [228]; found: 229.

Step 6) 4-Propargyloxy-3-(4-methoxyphenyl)benzaldehyde:

20 A solution of 4-hydroxy-3-(4-methoxyphenyl)benzaldehyde (1.14 g, 5 mmol) in DMF (10 mL) was treated with potassium carbonate (2.48 g, 18 mmol), potassium iodide (10 mg) and propargyl bromide (0.67 mL, 6 mmol). The mixture was heated at 80 C for 3 days, then cooled and the solvent removed under reduced pressure. The residue was redissolved in ethyl acetate and washed water then  
25 brine. The organic layer was dried over sodium sulphate then the solvent removed under reduced pressure and the residue purified by column chromatography (3/1 hexane/ethyl acetate) to afford 0.078 g of title compound.



Mass (calculated): [266]; found: 267.

30 NMR (400 MHz,  $\text{CDCl}_3$ ): 2.45 (1H, t,  $J = 1$  Hz,  $\text{C}\equiv\text{CH}$ ); 3.75 (3H, s,  $\text{CH}_3\text{O}$ ); 4.7 (2H, d,  $J = 1$  Hz,  $\text{C}\equiv\text{CCH}_2\text{O}$ ); 6.85 (2H, d,  $J = 8$  Hz, aryl-H); 7.15 (1H, d,  $J = 8$  Hz, aryl-H); 7.4 (2H, d,  $J = 8$  Hz, aryl-H); 7.75-7.85 (2H, m, aryl-H).

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Step 7) (R)-N-(1-Phenylethyl)-N-((4-propargyloxy-3-(4'-methoxyphenyl)phenylmethyl)amine:

The title compound was prepared from 4-propargyloxy-3-(4-methoxyphenyl)-  
5 benzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

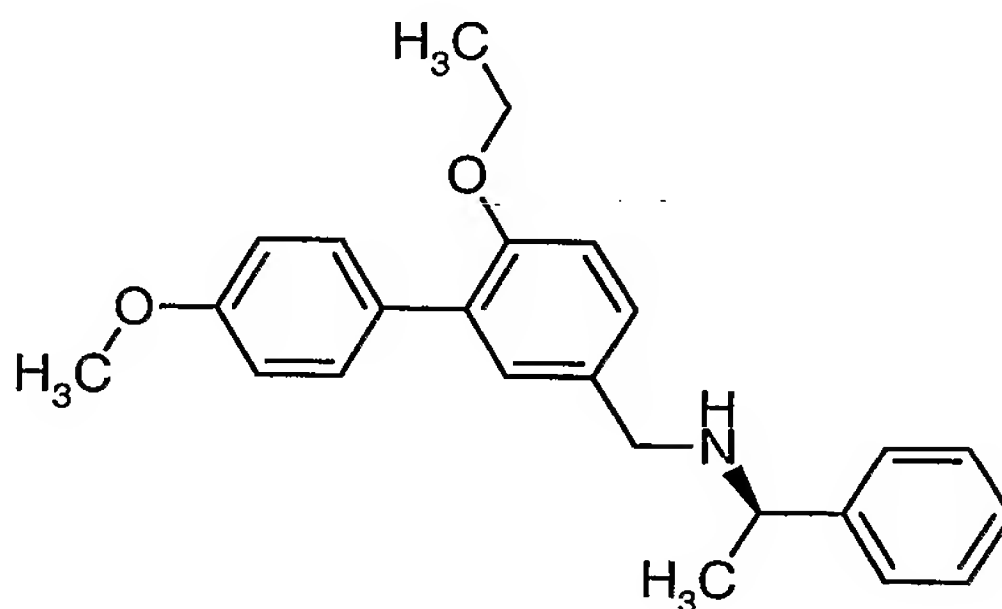
$C_{25}H_{25}NO_2$

Mass (calculated): [371]; (found):  $[M+H^+] = 372$ .

NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 2.3 (1H, t,  $J = 1$  Hz,  $C\equiv CH$ ); 3.5 and 3.55 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.75-3.8 (4H, m,  $NCHMe$  and  
10 MeO); 4.55 (2H, d,  $J = 1$  Hz,  $C\equiv CCH_2O$ ); 6.85 (2H, d,  $J = 8$  Hz, aryl-H); 7 (1H, d,  $J = 8$  Hz, aryl-H); 7.1-7.2 (3H, m, aryl-H); 7.25-7.35 (4H, m, aryl-H); 7.4 (2H, d,  $J = 8$  Hz, aryl-H).

**Example 38**

15 (R)-N-(1-Phenylethyl)-N-((4-ethoxy-3-(4'-methoxyphenyl)phenylmethyl)amine



Step 1) 4-Ethoxy-3-(4-methoxyphenyl)benzaldehyde:

A solution of 4-hydroxy-3-(4-methoxyphenyl)benzaldehyde (0.5 g, 2.19 mmol) in  
20 DMF (5 mL) was treated with potassium carbonate (0.9 g, 6.57 mmol), potassium iodide (10 mg) and ethyl iodide (0.21 mL, 0.263 mmol). The mixture was heated at 80 °C for 3 days, then cooled and the solvent removed under reduced pressure. The residue was redissolved in ethyl acetate and washed water then brine. The organic layer was dried over sodium sulphate then the solvent removed under  
25 reduced pressure and the residue purified by column chromatography (3/1 hexane/ethyl acetate) to afford 0.043 g of title compound.

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Mass (calculated): [256]; found: 257.

NMR (400 MHz,  $\text{CDCl}_3$ ): 1.3 (3H, t,  $J = 6$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ); 3.75 (3H, s,  $\text{CH}_3\text{O}$ ); 4.1 (2H, q,  $J = 6$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ); 6.85 (2H, d,  $J = 8$  Hz, aryl-H); 6.95 (1H, d,  $J = 8$  Hz, aryl-H); 7.4 (2H, d,  $J = 8$  Hz, aryl-H); 7.7 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.75 (1H, d,  $J = 1$  Hz, aryl-H).

Step 2) (R)-N-(1-Phenylethyl)-N-((4-ethoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine

10 The title compound was prepared from 4-ethoxy-3-(4-methoxyphenyl)benzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.



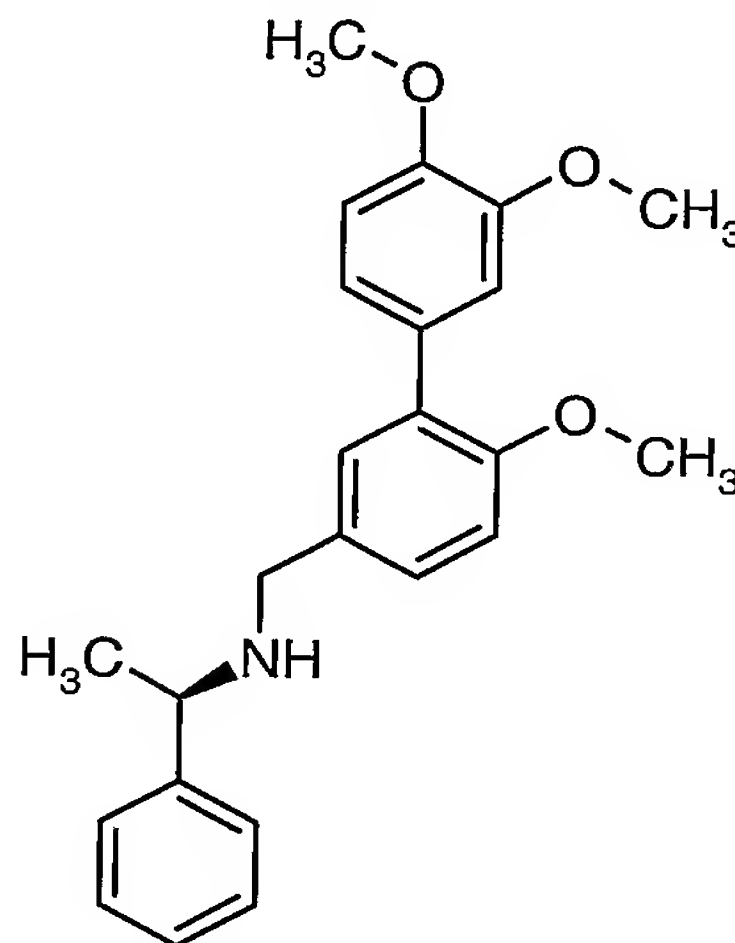
Mass (calculated): [361]; (found):  $[\text{M}+\text{H}^+] = 362$ .

15 NMR (400 MHz,  $\text{CDCl}_3$ ): 1.25 (3H, t,  $J = 6$  Hz,  $\text{OCH}_2\text{CH}_3$ ) 1.3 (3H, d,  $J = 6$  Hz,  $\text{NCHCH}_3$ ); 3.5 and 3.55 (2H, dd,  $J=12$  Hz,  $\text{CH}_2\text{N}$ ); 3.75-3.8 (4H, m,  $\text{NCHMe}$  and  $\text{MeO}$ ); 3.95 (2H, q,  $J = 6$  Hz,  $\text{OCH}_2\text{CH}_3$ ); 6.8 (1H, d,  $J = 8$  Hz, aryl-H); 6.85 (2H, d,  $J = 8$  Hz, aryl-H); 7.15-7.35 (2H, m, aryl-H); 7.35-7.4 (4H, m, aryl-H); 7.45 (2H, d,  $J = 8$  Hz, aryl-H).

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**Example 39**

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(3,4-dimethoxyphenyl)phenyl)methyl)amine



5

Step 1) 4-Methoxy-3-(3,4-dimethoxyphenyl)benzenecarboxaldehyde:

To a degassed solution of 3,4-dimethoxybenzeneboronic acid (2.18 g, 12 mmol), 3-bromo-4-methoxybenzaldehyde (3.23 g, 15 mmol) and potassium carbonate (5.18 g, 37.5 mmol) in toluene/ethanol 2/1 (72 mL), Pd(PPh<sub>3</sub>)<sub>4</sub> (173 mg, 1.2 mol%) was added and the mixture was degassed for further 5 minutes. The mixture was then refluxed for 15 hours. The solid was filtered off and the filtrate concentrated under reduced pressure. The residue was dissolved in AcOEt, partitioned between ethyl acetate and water and extracted then washed with brine. The organic solvent was dried over sodium sulphate, removed under reduced pressure, and the residue purified by column chromatography (heptane/ethyl acetate 1/1) to afford 2.95 of title compound.

C<sub>16</sub>H<sub>16</sub>O<sub>4</sub>

Mass (calculated): [272]; found: 273.

NMR (400 MHz, CDCl<sub>3</sub>): 3.85-3.87 (9H, 3s, 3 CH<sub>3</sub>O); 6.9 (1H, d, *J* = 8 Hz, aryl-H); 6.9-7.05 (3H, m, aryl-H); 7.85-7.9 (2H, m, aryl-H); 9.85 (1H, s, CHO).

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Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(3,4-dimethoxyphenyl)-phenylmethyl)amine:

The title compound was prepared from 4-methoxy-3-(3,4-dimethoxyphenyl)benzenecarboxaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

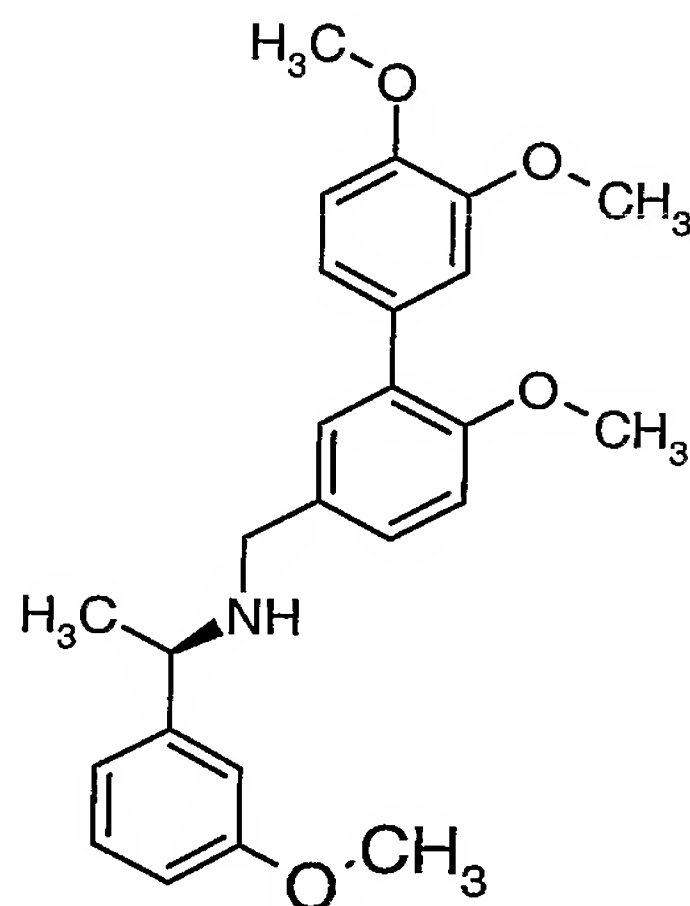


Mass (calculated): [377]; (found):  $[\text{M}+\text{H}^+] = 378$ .

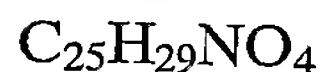
NMR (400 MHz,  $\text{CDCl}_3$ ): 1.3 (3H, t,  $J = 6$  Hz,  $\text{NCHCH}_3$ ); 3.55 and 3.6 (2H, dd,  $J=12$  Hz,  $\text{CH}_2\text{N}$ ); 3.7 (3H, s,  $\text{CH}_3\text{O}$ ); 3.8-4 (7H, m,  $\text{NCHMe}$  and 2 MeO); 6.8-6.85 (2H, m, aryl-H); 6.95-7.05 (2H, m, aryl-H); 7.1-7.15 (2H, m, aryl-H); 7.25-7.4 (4H, m, aryl-H).

**Example 40**

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(3,4-dimethoxyphenyl)phenylmethyl)amine



The title compound was prepared from 4-methoxy-3-(3,4-dimethoxyphenyl)benzenecarboxaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.



Mass (calculated): [407]; (found):  $[\text{M}+\text{H}^+] = 408$ .

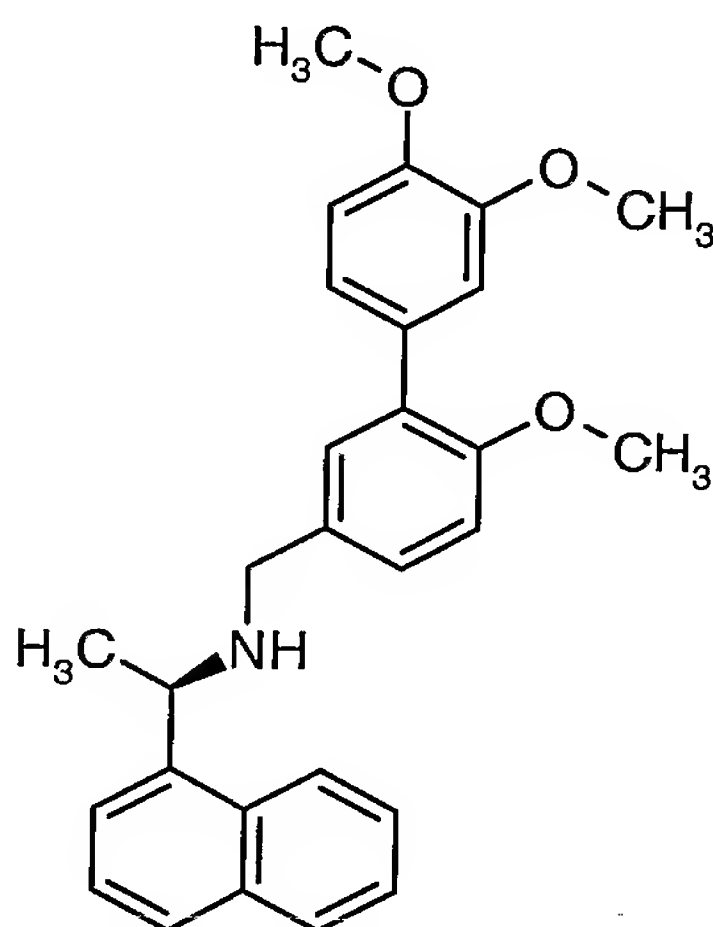
- 74 -

NMR (400 MHz, CDCl<sub>3</sub>): 1.3 (3H, t,  $J = 6$  Hz, NCHCH<sub>3</sub>); 3.55 and 3.6 (2H, dd,  $J=12$  Hz, CH<sub>2</sub>N); 3.7 and 3.72 (6H, 2 s, 2 CH<sub>3</sub>O); 3.8-3.9 (4H, m, NCHMe and CH<sub>3</sub>O); 6.8 (1H, dd,  $J = 2$  and 8 Hz, aryl-H); 6.8-6.9 (2H, m, aryl-H); 6.9-7 (2H, m, aryl-H); 7-7.05 (2H, m, aryl-H); 7.15-7.3 (3H, m, aryl-H).

5

**Example 41**

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(3,4-dimethoxyphenyl)-phenyl)methyl)amine



10

The title compound was prepared from 4-methoxy-3-(3,4-dimethoxyphenyl) benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

C<sub>28</sub>H<sub>29</sub>NO<sub>3</sub>

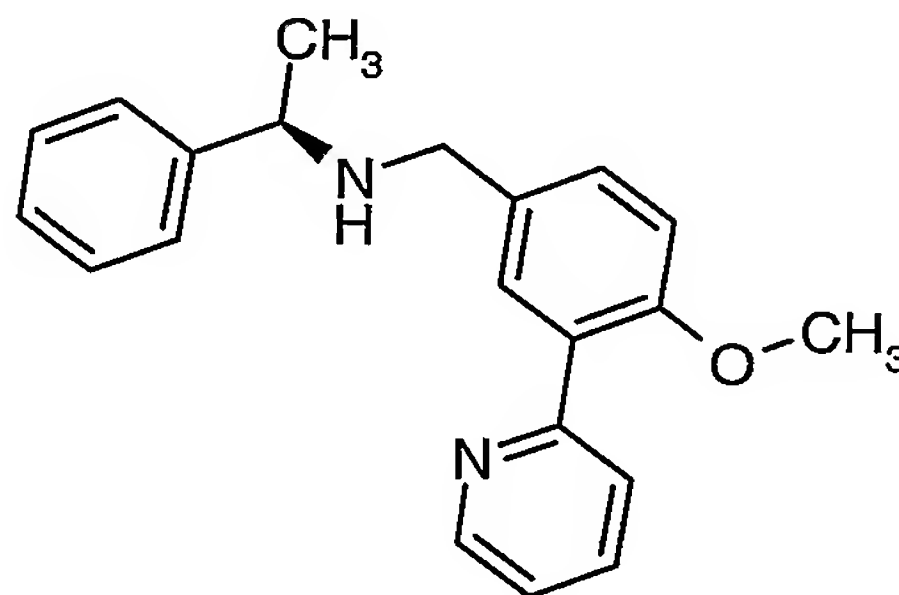
15 Mass (calculated): [427]; (found): [M+H<sup>+</sup>] = 428, 257, 155.

NMR (400 MHz, CDCl<sub>3</sub>): 1.4 (3H, t,  $J = 6$  Hz, NCHCH<sub>3</sub>); 3.55 and 3.6 (2H, dd,  $J=12$  Hz, CH<sub>2</sub>N); 3.7 (3H, s, CH<sub>3</sub>O); 3.8 and 3.82 (6H, 2 s, 2 CH<sub>3</sub>O); 6.8-6.85 (2H, m, aryl-H); 6.95-7.0 (2H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.3-7.5 (3H, m, aryl-H); 7.65-7.7 (2H, m, aryl-H); 7.75-7.8 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

20



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**Example 42****(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-2-yl)phenyl)methyl)amine**

5

Step 1) 4-Methoxy-3-(pyrid-2-yl)benzenecarboxaldehyde:

A degassed solution of 2-bromopyridine (1.0 g, 6.33 mmol), 3-borono-4-methoxybenzaldehyde (1.37 g, 7.6 mmol) and [(PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>] (64 mg, 0.09 mmol) in dimethoxyethane (30 mL), methanol (5 mL) and Na<sub>2</sub>CO<sub>3</sub> (2M, 20 mL) was heated at 75 °C for 16 hours. The mixture was then cooled, diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate and the solvent removed under reduced pressure. The crude was purified by column chromatography (heptane/AcOEt 7/3 to 6/4) to afford 1.31 g of title compound.

C<sub>13</sub>H<sub>11</sub>NO<sub>2</sub>15 Mass (calculated): [213]; (found) [M+H<sup>+</sup>] = 214.

NMR (400 MHz, CDCl<sub>3</sub>): 3.85 (3H, s, MeO); 7.05 (1H, d, *J* = 8 Hz, aryl/pyridyl-H); 7.2 (1H, m, aryl/pyridyl -H); 7.65 (1H, m, aryl/pyridyl -H); 7.75 (1H, m, aryl/pyridyl-H); 7.85 (1H, m, aryl/pyridyl-H); 8.2 (1H, s, aryl/pyridyl-H); 8.65 (1H, s, aryl/pyridyl-H); 9.9 (1H, s, CHO).

20

Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-2-yl)phenyl)methyl)amine

The title compound was prepared from 4-methoxy-3-(pyrid-2-yl)benzenecarboxaldehyde and (R)-α-methylbenzylamine according to general procedure C.

25 C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O

Mass (calculated): [318]; (found): [M+H<sup>+</sup>] = 319, 198.

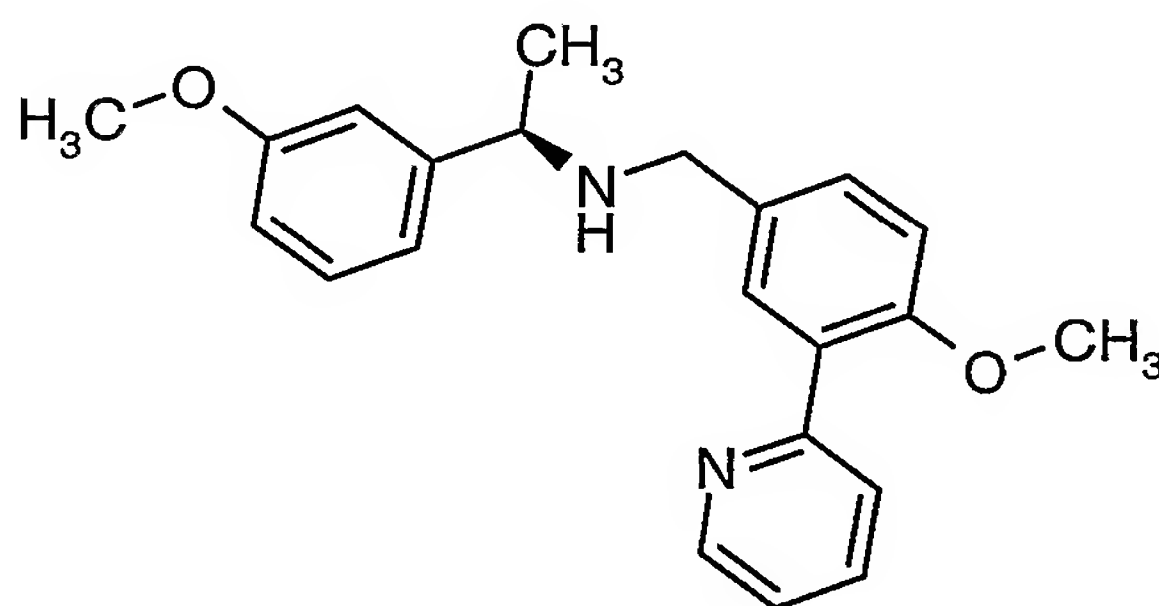
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NMR (400 MHz, CDCl<sub>3</sub>): 1.3 (3H, d,  $J = 6$  Hz, NCHCH<sub>3</sub>); 3.5 and 3.55 (2H, dd,  $J = 12$  Hz, CH<sub>2</sub>N); 3.7 (3H, s, MeO); 3.75 (1H, q,  $J = 7$  Hz; NCHMe); 6.8 (1H, d,  $J = 8$  Hz, aryl-H); 7.05-7.1 (1H, m, aryl-H); 7.15-7.35 (6H, m, aryl-H); 7.55-7.6 (2H, m, aryl-H); 7.7 (1H, d,  $J = 8$  Hz, aryl-H); 8.55-8.6 (1H, m, pyridyl-H).

5

**Example 43**

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(pyrid-2-yl)phenyl)methyl)amine



10

The title compound was prepared from 4-methoxy-3-(pyrid-2-yl)benzenecarboxaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

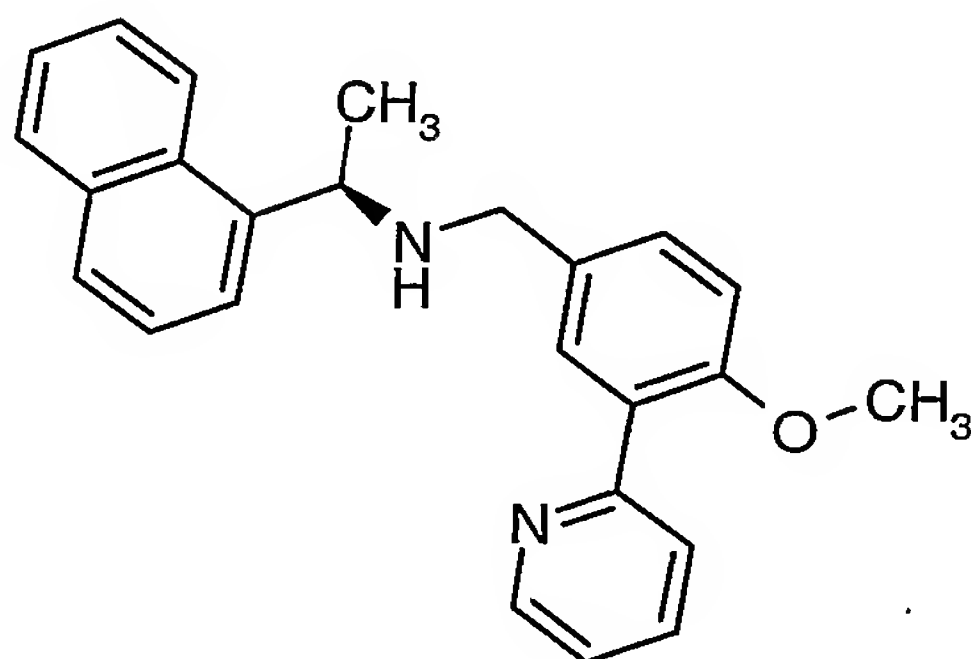
C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>

15 Mass (calculated): [348]; (found): [M+H<sup>+</sup>] = 349, 198.

NMR (400 MHz, CDCl<sub>3</sub>): 1.3 (3H, d,  $J = 6$  Hz, NCHCH<sub>3</sub>); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz, CH<sub>2</sub>N); 3.7-3.8 (7H, m, 2 MeO and NCHMe); 6.7 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.8-6.9 (3H, m, aryl-H); 7.05-7.3 (3H, m, aryl-H); 7.55-7.65 (2H, m, aryl-H); 7.75 (1H, d,  $J = 8$  Hz, aryl-H); 7.7 (1H, d,  $J = 8$  Hz, aryl-H); 8.6 (1H, m, pyridyl-H).

20

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**Example 44****(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(pyrid-2-yl)phenyl)methyl)amine**

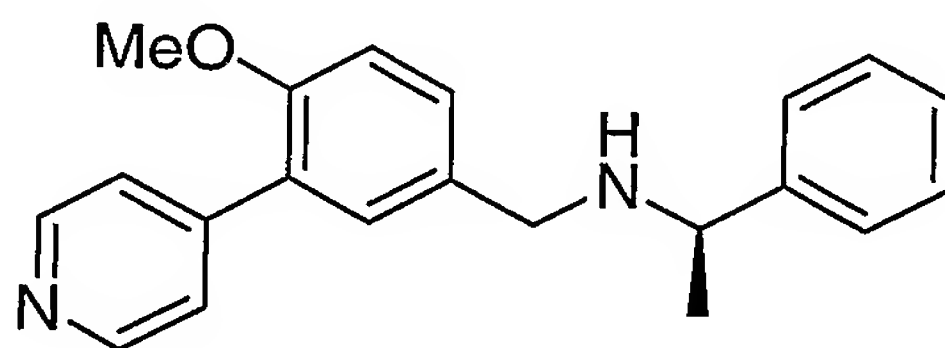
- 5 The title compound was prepared from 4-methoxy-3-(pyrid-2-yl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{25}H_{24}N_2O$

Mass (calculated): [368]; (found):  $[M+H^+] = 369, 198$ .

- 10 NMR (400 MHz,  $CDCl_3$ ): 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.75 (3H, s, MeO); 4.65 (1H, q,  $J = 7$  Hz;  $NCHMe$ ); 6.8 (1H, d,  $J = 8$  Hz, aryl-H); 7.05-7.1 (1H, m, aryl-H); 7.15-7.25 (1H, m, aryl-H); 7.3-7.45 (3H, m, aryl-H); 7.5-7.6 (2H, m, aryl-H); 7.6-7.75 (3H, m, aryl-H); 7.75-7.8 (1H, m, aryl-H); 8-8.05 (1H, m, aryl-H); 8.55-8.6 (1H, m, pyridyl-H).

15

**Example 45****(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-4-yl)phenyl)methyl)amine**

20

Step 1) 4-Methoxy-3-(pyrid-4-yl)benzenecarboxaldehyde:

A degassed solution of 4-bromopyridine hydrochloride (1.36 g, 7 mmol), 3-borono-4-methoxybenzaldehyde (1.37 g, 7.6 mmol) and  $[(PPh_3)_2PdCl_2]$  (246 mg, 0.35 mmol) in dimethoxyethane (30 mL), methanol (5 mL) and  $Na_2CO_3$  (2M, 20

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mL) was heated at 75 °C for 16 hours. The mixture was then cooled, diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate and the solvent removed under reduced pressure. The crude was purified by column chromatography (heptane/AcOEt 3/1) to afford 1.18 g of title compound

5  $C_{13}H_{11}NO_2$

Mass (calculated): [213]; (found)  $[M+H^+] = 214$ .

NMR (400 MHz,  $CDCl_3$ ): 3.85 (3H, s, MeO); 7.05 (1H, d,  $J = 8$  Hz, aryl-H); 7.4 (2H, d,  $J = 7$  Hz, pyridyl-H); 7.8 (1H, d,  $J = 1$  Hz, aryl-H); 7.85 (1H, dd,  $J = 1$  and 8 Hz); 8.6 (2H, d,  $J = 7$  Hz, pyridyl-H).

10

Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-4-yl)phenylmethyl)amine:

The title compound was prepared from 4-methoxy-3-(pyrid-4-yl)benzenecarboxaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

$C_{21}H_{22}N_2O$

15 Mass (calculated): [318]; (found):  $[M+H^+] = 319, 215$ .

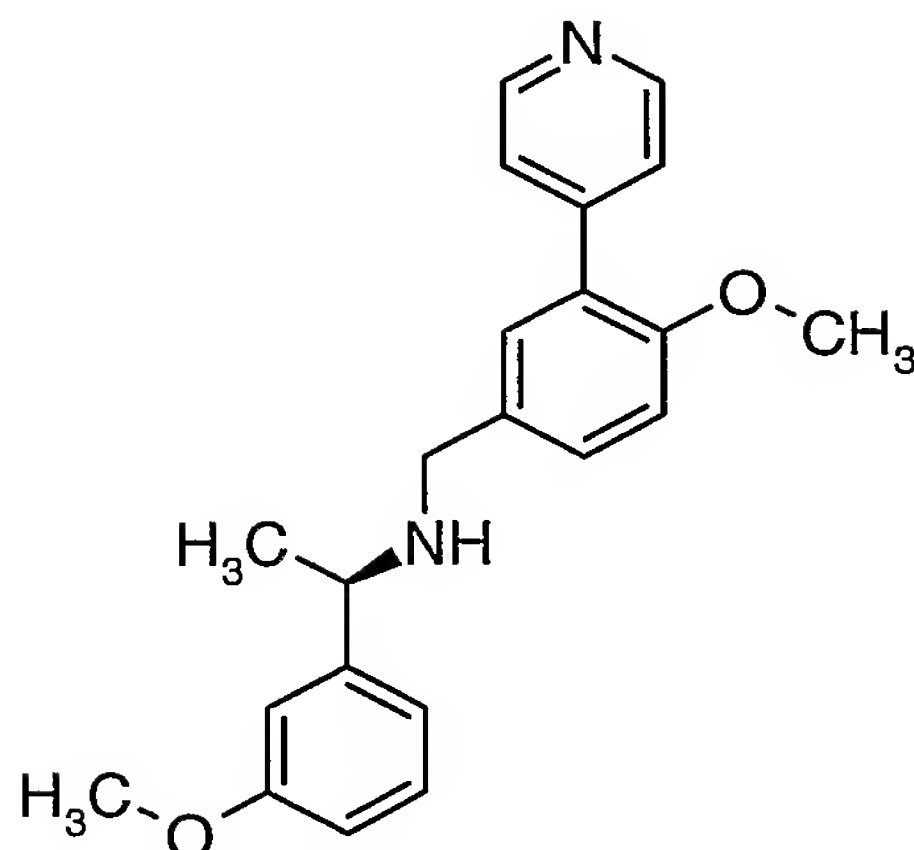
NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 (2H, bq,  $CH_2N$ ); 3.75 (3H, s, MeO); 3.8 (1H, bq,  $NCHMe$ ); 6.85 (1H, d,  $J = 8$  Hz, aryl-H); 7.15-7.25 (3H, m, aryl-H); 7.25-7.3 (4H, m, aryl-H); 7.45 (2H, bs, pyridyl-H); 8.4-8.6 (2H, bs, pyridyl-H).

20

#### Example 46

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(pyrid-4-yl)phenylmethyl)amine

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The title compound was prepared from 4-methoxy-3-(pyrid-4-yl)benzene-carboxaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

5  $C_{22}H_{24}N_2O_2$

Mass (calculated): [348]; (found):  $[M+H^+] = 349, 215$ .

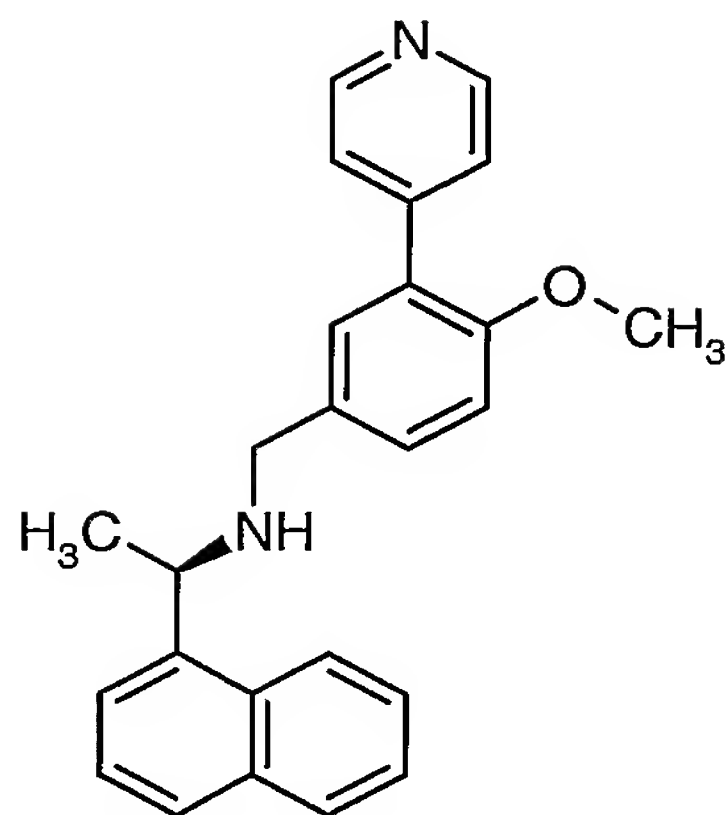
NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 7$  Hz,  $NCHCH_3$ ); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.75 (3H, s, MeO); 3.8 (1H, q,  $J = 7$  Hz,  $NCHMe$ ); 6.75 (1H, d,  $J = 8$  Hz, aryl-H); 6.85-6.9 (3H, m, aryl-H); 7.15-7.25 (3H, m, aryl-H); 7.4 (2H, bd, pyridyl-H); 8.5 (2H, bs, pyridyl-H).

10

#### Example 47

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(pyrid-4-yl)phenyl)methyl)amine

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The title compound was prepared from 4-methoxy-3-(pyrid-4-yl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

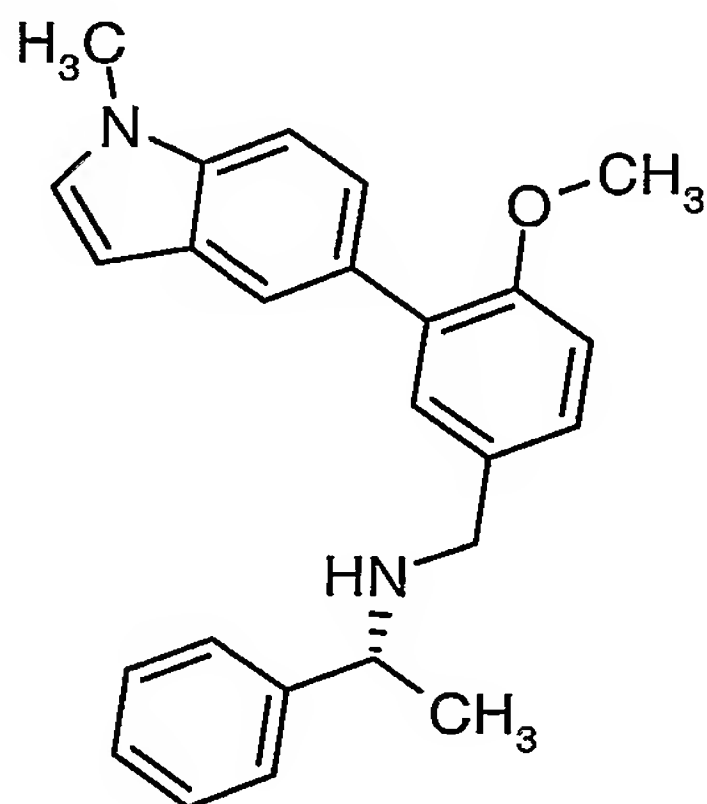
5  $C_{25}H_{24}N_2O$

Mass (calculated): [368]; (found):  $[M+H^+] = 369, 215$ .

NMR (400 MHz,  $CDCl_3$ ): 1.5 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.75 (3H, s, MeO); 4.7 (1H, bq,  $NCHMe$ ); 6.85 (1H, d,  $J = 8$  Hz, aryl-H); 7.15 (1H, d,  $J = 1$  Hz, aryl-H); 7.3 (1H, dd,  $J = 1$  and 8 Hz, aryl-H);  
 10 7.35 (2H, d,  $J = 5$  Hz, pyridyl-H); 7.35-7.5 (3H, m, aryl-H); 7.65-7.7 (2H, m, aryl-H); 7.85 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 8 (1H, d,  $J = 8$  Hz, aryl-H); 8.5 (2H, bd, pyridyl-H).

### Example 48

15 ((1R)-1-Phenylethyl){[4-methoxy-3-(1-methylindol-5-yl)phenyl]methyl}amine



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Step 1) 3-(Indol-5-yl)-4-methoxybenzaldehyde:

A solution of 5-formyl-2-methoxybenzeneboronic acid (5 g, 28.5 mmol) 5-  
bromoindole (5 g, 25.5 mmol) and  $K_2CO_3$  (7.7 g, 56 mmol) in ethanol (25 mL)  
and toluene (50 mL) was degassed prior to addition of  $Pd(Ph_3)_4$  (300 mg, 0.25  
mmol). The mixture was refluxed for 16 hours then cooled and concentrated in  
vacuo, extracted with dichloromethane, washed with water and the organic layer  
dried over sodium sulphate. The crude was purified by column chromatography  
(hexane/ethyl acetate 6/4) to give 4.5 g of title compound.



Mass (calculated): [251]; (found):  $[M+H^+] = 252$ .

NMR (400 MHz,  $CDCl_3$ ): 3.75 (3H, s,  $CH_3O$ ); 6.45 (1H, m, indole-H); 6.95 (1H,  
d,  $J = 8$  Hz, aryl-H); 7.05-7.15 (1H, m, aryl-H); 7.3 (1H, dd,  $J = 1$  and 8 Hz, aryl-  
H); 7.4 (1H, d,  $J = 8$  Hz, aryl-H); 7.65 (1H, s, aryl-H); 7.7 (1H, dd,  $J = 1$  and 8 Hz,  
aryl-H); 7.75 (1H, d,  $J = 1$  Hz, aryl-H); 8.1 (1H, bs, NH); 9.8 (1H, s, CHO).

Step 2) 3-(1-Methylindol-5-yl)-4-methoxybenzaldehyde:

A solution of 3-(indol-5-yl)-4-methoxybenzaldehyde (0.50 g, 2.0 mmol) in DMF  
(10 mL) was cooled to 0 °C and NaH (60% dispersion in mineral oil, 0.14 g, 3.0  
mmol) was added. The mixture was stirred at 0 °C for 45 minutes, then methyl  
iodide (0.34 g, 4.4 mmol) was added and the reaction was stirred for 16 hours at  
room temperature. The mixture was then poured into water and extracted with  
ethyl acetate, washed with water and dried over sodium sulphate. The solvent was  
removed in vacuo and the crude was purified by column chromatography  
(hexane/ethyl acetate 7/3) to give 0.48 g of title compound.



Mass (calculated): [265]; (found):  $[M+H^+] = 266$ .

NMR (400 MHz,  $CDCl_3$ ): 3.85 (3H, s,  $CH_3O$ ); 3.95 (3H, s,  $CH_3N$ ); 6.65 (1H, m,  
indole-H); 7.10-7.25 (2H, m, aryl-H); 7.4-7.5 (2H, m, aryl-H); 7.8 (1H, s, aryl-H);  
7.9 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 8 (1H, d,  $J = 1$  Hz, aryl-H); 10 (1H, s, CHO).

Step 3) ((1R)-1-Phenylethyl){[4-methoxy-3-(1-methylindol-5-yl)phenyl]methyl}amine:



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The title compound was prepared from 3-(1-methylindol-5-yl)-4-methoxybenzaldehyde and (R)- $\alpha$ -methylbenzylamine according to general procedure C.

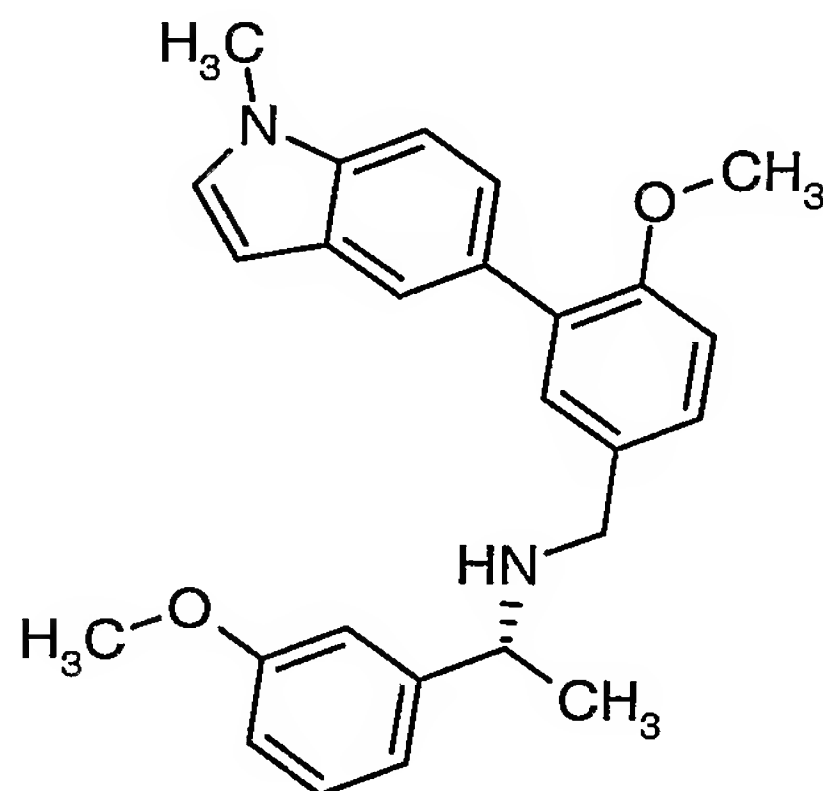
$C_{25}H_{26}N_2O$

5 Mass (calculated): [370]; (found):  $[M+H^+] = 371, 250$ .

### Example 49

[(1R)-1-(3-Methoxyphenyl)ethyl]{[4-methoxy-3-(1-methylindol-5-yl)phenyl]methyl}amine

10



The title compound was prepared from 3-(1-methylindol-5-yl)-4-methoxybenzaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

15  $C_{26}H_{28}N_2O_2$

Mass (calculated): [400]; (found):  $[M+H^+] = 401$ .

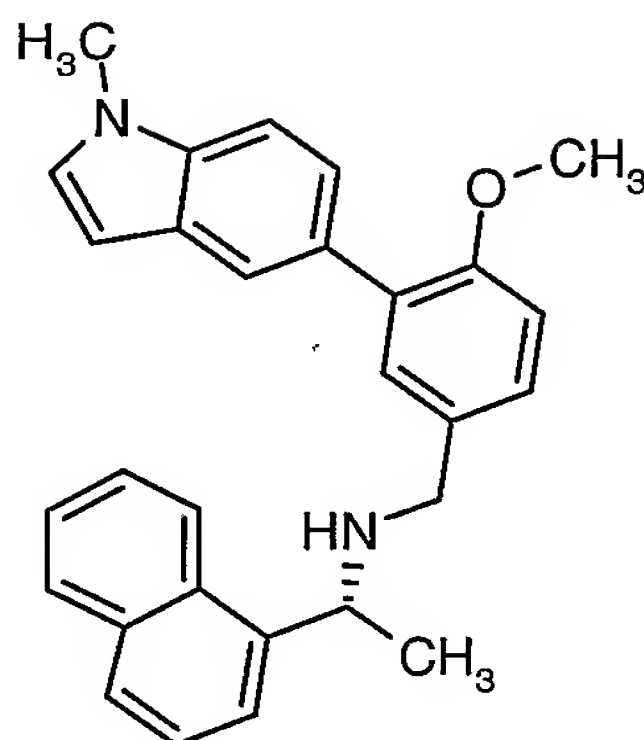
NMR (400 MHz,  $CDCl_3$ ): 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.55 and 3.6 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.65-3.8 (10H, m, 3 MeO and  $NCHMe$ ); 6.4 (1H, d,  $J = 5$  Hz, indole-H); 6.7 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.8-6.9 (3H, m, aryl-H); 6.95 (1H, d,  $J = 2$  Hz, aryl-H); 7.1-7.3 (4H, m, aryl-H); 7.35 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.65 (1H, d,  $J = 1$  Hz, aryl-H).

20

### Example 50

((1R)-1-Naphthylethyl){[4-methoxy-3-(1-methylindol-5-yl)phenyl]methyl}amine

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The title compound was prepared from 3-(1-methylindol-5-yl)-4-methoxybenzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

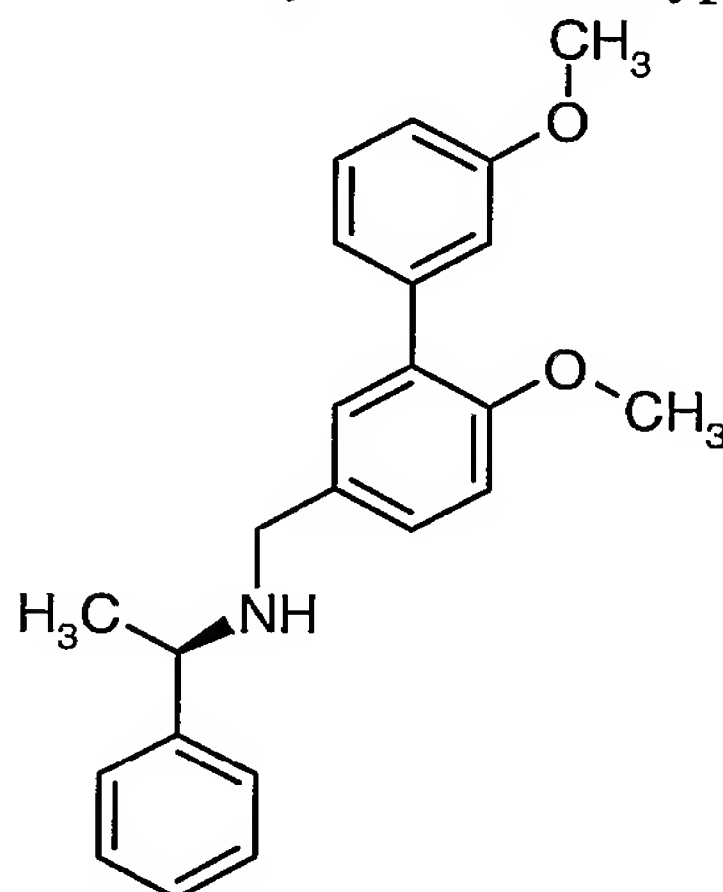
5  $C_{29}H_{28}N_2O$

Mass (calculated): [420]; (found):  $[M+H^+] = 421$ .

NMR (400 MHz,  $CDCl_3$ ): 1.6 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.8 and 3.85 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.85 and 3.87 (6H, m, 2 MeO); 4.8 (1H, q,  $J = 6$  Hz,  $NCHMe$ ); 6.6 (1H, d,  $J = 5$  Hz, indole-H); 7 (1H, d,  $J = 8$  Hz, aryl-H); 7.1 (1H, d,  $J = 1$  Hz, aryl-H); 7.3 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.35-7.4 (2H, m, aryl-H); 7.5 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.5-7.6 (3H, m, aryl-H); 7.8-7.9 (3H, m, aryl-H); 7.95-7.8 (1H, m, aryl-H); 8.2-8.3 (1H, m, aryl-H).

### Example 51

15 (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(3-methoxyphenyl)phenyl)methyl)amine



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Step 1) 4-Methoxy-3-(3-methoxyphenyl)benzenecarboxaldehyde:

A degassed solution of 3-bromoanisole (1.31 g, 7 mmol), 3-borono-4-methoxybenzaldehyde (1.38 g, 7.4 mmol) and [(PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>] (246 mg, 0.35 mmol) in dimethoxyethane (35 mL), methanol and Na<sub>2</sub>CO<sub>3</sub> 2M (20 mL) was heated at 75 °C for 24 hours. The mixture was then cooled, diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and the solvent removed under reduced pressure. The crude was purified by column chromatography (heptane/AcOEt 4/1) to afford 1.14 g of title compound.

C<sub>15</sub>H<sub>14</sub>O<sub>3</sub>

Mass (calculated): [242]; (found): [M+H<sup>+</sup>] = 243; [M+H<sup>+</sup>+MeCN] = 284.  
NMR (400 MHz, CDCl<sub>3</sub>): 3.85 (3H, s, MeO); 3.95 (3H, s, MeO); 6.9 (1H, dd, *J* = 1 and 8 Hz, aryl-H); 7.05-7.15 (1H, m, aryl-H); 7.35 (1H, t, *J* = 8 Hz, aryl-H); 7.85-7.95 (2H, m, aryl-H); 9.85 (1H, s, CHO).

Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(3-methoxyphenyl)phenyl)methyl)amine:

The title compound was prepared from 4-methoxy-3-(3-methoxyphenyl)benzenecarboxaldehyde and (R)-α-methylbenzylamine according to general procedure C.

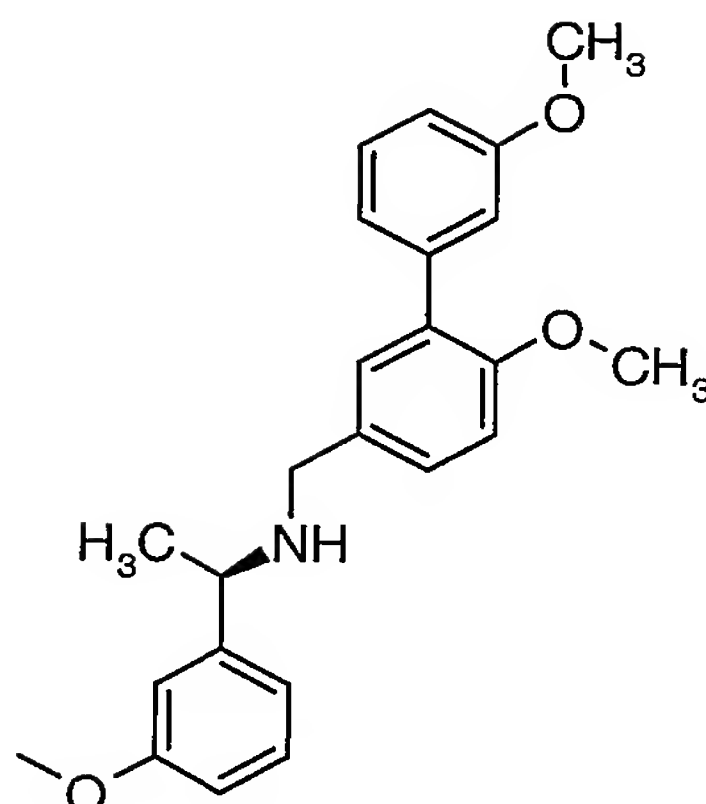
C<sub>23</sub>H<sub>25</sub>NO<sub>2</sub>

Mass (calculated): [347]; (found): [M+H<sup>+</sup>] = 348.  
NMR (400 MHz, CDCl<sub>3</sub>): 1.3 (3H, d, *J* = 6 Hz, NCHCH<sub>3</sub>); 3.5 and 3.55 (2H, dd, *J* = 12 Hz, CH<sub>2</sub>N); 3.7 (3H, s, MeO); 3.75-3.85 (4H, m, NCHMe and MeO); 6.75-6.9 (2H, m, aryl-H); 7-7.1 (2H, m, aryl-H); 7.1-7.2 (3H, m, aryl-H); 7.2-7.3 (5H, m, aryl-H).

**Example 52**

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(3-methoxyphenyl)phenyl)methyl)amine

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The title compound was prepared from 4-methoxy-3-(3-methoxyphenyl)benzene-carboxaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure C.

5  $C_{24}H_{27}NO_3$

Mass (calculated): [377]; (found):  $[M+H^+] = 378$ .

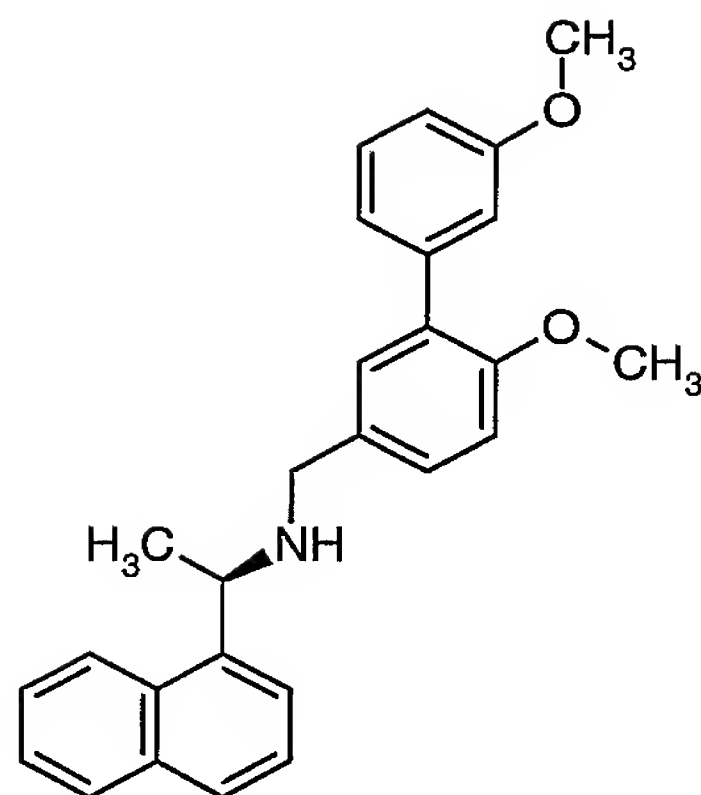
NMR (400 MHz,  $CDCl_3$ ): 1.4 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.8-3.9 (10H, 3 s and m,  $NCHMe$  and 3 MeO); 6.8 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.9 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.95-7 (3H, m, aryl-H);

10 7.1-7.2 (2H, m, aryl-H); 7.2-7.4 (4H, m, aryl-H).

### Example 53

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(3-methoxyphenyl)phenylmethyl)amine

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The title compound was prepared from 4-methoxy-3-(3-methoxyphenyl)benzene-carboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general  
 5 procedure C.

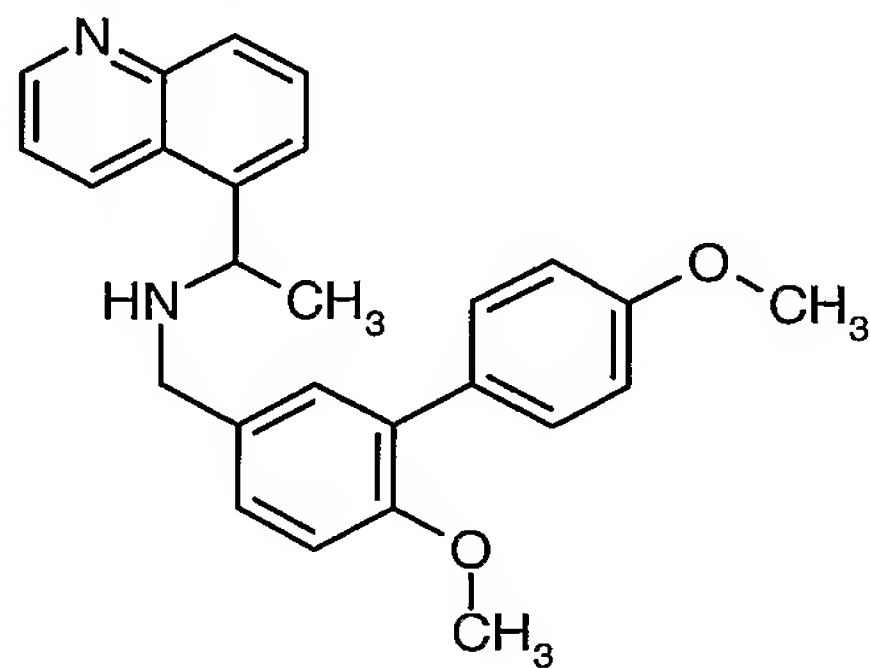
$C_{27}H_{27}NO_2$

Mass (calculated): [397]; (found):  $[M+H^+] = 398$ .

NMR (400 MHz,  $CDCl_3$ ): 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7 and 3.75 (6H, 2 s, 2 MeO); 4.65 (1H, q,  $J = 6$  Hz,  $NCHMe$ ); 6.75-6.9 (2H, m, aryl-H); 7-7.1 (2H, m, aryl-H); 7.1-7.25 (3H, m, aryl-H); 7.4-7.45 (3H, m, aryl-H); 7.7 (2H, d,  $J = 8$  Hz, aryl-H); 7.75-7.8 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

### Example 54

*N*-(1-(Quinol-5-yl)ethyl)-*N*-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



Step 1) 5-Trifluoromethanesulphonyloxyquinoline:

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A solution of 5-hydroxyquinoline (0.5 g, 3.4 mmol) in DCM (5 mL) was treated with pyridine (1.08 g, 13.7 mmol) and then trifluoromethanesulphone anhydride (1.1 g, 4.12 mmol). The mixture was stirred overnight then diluted with dichloromethane and washed with water. The organic layer was concentrated under reduced pressure and the excess pyridine azeotropically removed with toluene, to afford 0.47 g of title compound.

Step 2) 5-Acetylquinoline:

A degassed solution of 5-trifluoromethanesulphonyloxyquinoline (0.41 g, 1.47 mmol), butyl vinyl ether (0.38 mL, 2.94 mmol), palladium acetate (10 mg, 0.043 mmol), potassium carbonate (0.24 g, 1.76 mmol), 1,3-bis(diphenylphosphino)propane (40 mg, 0.097 mmol) in DMF (3.67 mL) and water (0.88 mL) was heated in a sealed tube at 100 °C for 16 hours.. The reaction mixture was then cooled and treated with 1M HCl and the mixture stirred for 30 minutes, then basified and extracted with dichloromethane. The organic layer was then evaporated under reduced pressure to afford the title compound.

Step 3) 4-Methoxy-3-(4-methoxyphenyl)benzyl alcohol:

A solution of 4-methoxy-3-(4-methoxyphenyl)benzenecarboxaldehyde (1 g, 4.13 mmol) in methanol (12 mL) was treated with polymer-supported borohydride (10.3 mmol) and the mixture shaken for 16 hours. The resin was then filtered and the filtrate concentrated under reduced pressure to afford 0.88 g of title compound.

Step 4) 4-Methoxy-3-(4-methoxyphenyl)benzylazide:

A solution of 4-methoxy-3-(4-methoxyphenyl)benzyl alcohol (0.88 g, 3.59 mmol) and diphenylphosphoryl azide (1.18 g, 4.32 mmol) in anhydrous THF (15 mL) was cooled in an ice-bath prior to addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.87 g, 5.76 mmol). The resulting mixture was then stirred at room temperature for 48 hours. More diphenylphosphoryl azide was added (1.4 mol, 0.39 g) and the mixture stirred for further 16 hours. The solvent was then evaporated, the residue taken into dichloromethane and washed with acid. The organic layer was

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separated and the solvent removed under reduced pressure to afford 0.82 g of title compound.

Step 5) 4-Methoxy-3-(4-methoxyphenyl)benzylamine:

- 5 A solution of 4-methoxy-3-(4-methoxyphenyl)benzylazide (0.82 g, 3.07 mmol) in ethanol (50 mL) was hydrogenated under atmospheric pressure for 16 hours. The catalyst was filtered off, the solvent removed under reduced pressure and the crude purified by column chromatography (hexane/ethyl acetate 6/1) to afford 400 mg of title compound.

10  $C_{15}H_{17}NO_2$

Mass (calculated): [243]; found: 227 ( $MH^+ - NH_2$ ).

NMR (400 MHz,  $CDCl_3$ ): 3.65 (3H, s,  $CH_3O$ ); 3.7-3.8 (5H, m,  $CH_3O$  and aryl- $CH_2O$ ); 5.45 (2H, bs,  $NH_2$ ); 6.75-6.95 (3H, m, aryl-H); 7.1-7.25 (2H, m, aryl-H); 7.4 (2H, d,  $J = 8$  Hz, aryl-H).

15

Step 6) *N*-(1-(Quinol-5-yl)ethyl)-*N*-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine:

- A solution of 4-methoxy-3-(4-methoxyphenyl)benzylamine (243 mg, 1, mmol) and 5-acetylquinoline (152 mg, 0.89 mmol) in methanol (3 mL) was treated with  
20 acetic acid (0.05 mL) and polymer-supported cyanoborohydride (0.9 g, 2.25 mmol). The mixture was stirred at 50 C for 20 hours, then cooled. The solid was filtered off and the filtrate concentrated in vacuo. The crude was purified by column chromatography (AcOEt/cyHex 7/3 to 100%AcOEt) to afford 91 mg of title compound.

25  $C_{26}H_{26}N_2O_2$

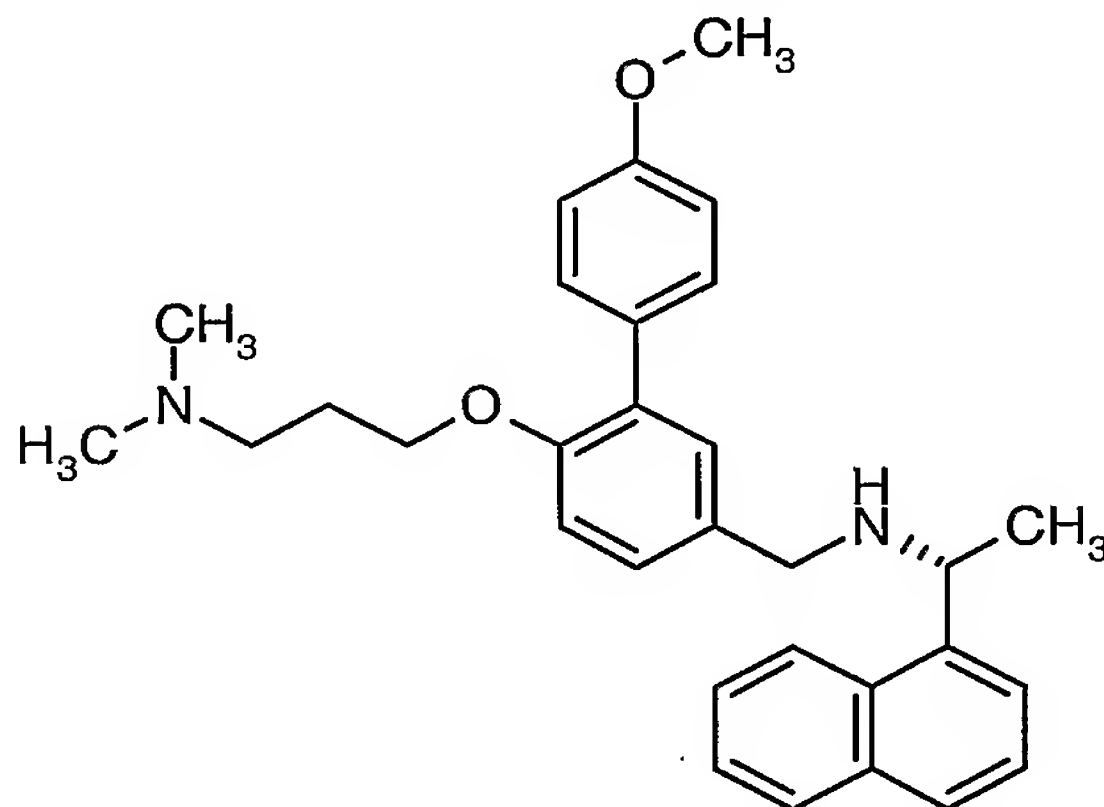
Mass (calculated): [398]; found: 399, 797.

- NMR (400 MHz,  $CDCl_3$ ): 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 and 3.65 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.7 and 3.75 (6H, 2 s, 2 MeO); 4.55 (1H, q,  $J = 6$  Hz,  $NCHCH_3$ ); 6.8-6.9 (3H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.3 (1H, dd,  $J = 4$   
30 and 8 Hz, aryl-H); 7.35 (2H,  $J = 8$  Hz, aryl-H); 7.75 (1H, t,  $J = 6$  Hz, aryl-H); 7.75 (1H, d,  $J = 8$  Hz, aryl-H); 7.95 (1H, d,  $J = 8$  Hz, aryl-H); 8.55 (1H, d,  $J = 8$  Hz, aryl-H); 8.8-8.9 (1H, m, aryl-H).



**Example 55**

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-(3-N,N-dimethylamino)propoxy-3-(4-methoxyphenyl)phenyl)methyl)amine



5

Step 1) 3-Bromo-4-(3-chloropropoxy)benzaldehyde:

A solution of 3-bromo-4-hydroxybenzaldehyde (1.88 g, 9.36 mmol) 1-bromo-3-chloropropane (9.25 mL, 93.6 mmol) and potassium carbonate (3.22 g, 23.4 mmol) in acetonitrile (15 mL) was heated at 80 C for 2 days. The solid was filtered through a plug of silica eluting with MeCN. The filtrate was evaporated to yield 2.46 g of title compound.

10

Step 2) 3-Bromo-4-(3-N,N-dimethylamino)propoxybenzaldehyde:

A suspension of 3-bromo-4-(3-chloropropoxy)benzaldehyde (2.47 g, 8.08 mmol) dimethylamine hydrochloride (6.58 g, 80.8 mmol) and potassium carbonate (11.1 g, 80.8 mmol) in acetonitrile (120 mL) was stirred for 2 days at room temperature, then more Me<sub>2</sub>NH HCl 6.58 g, 80.8 mmol) was added together with KI (50 mg). After 4 days the mixture was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water then brine. The organic layer was dried over MgSO<sub>4</sub> then evaporated to give a crude which was purified by column chromatography (DCM/MeOH 9/1) to give 1.24 g of title compound.

15

20



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Step 3) 4-(3-*N,N*-Dimethylamino)propoxy-3-(4-methoxyphenyl)benzaldehyde:

A solution of 4-methoxybenzeneboronic acid (0.79 g, 5.19 mmol), 3-bromo-4-(3-*N,N*-dimethylamino)propoxybenzaldehyde (1.28 g, 4.33 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.78 g, 12.9 mmol) in ethanol (12 mL) and toluene (24 mL) was degassed prior to addition of Pd(Ph<sub>3</sub>)<sub>4</sub> (100 mg, 1 mmol%). The mixture was refluxed for 18 hours then cooled and filtered through diatomaceous earth. The filtrate was concentrated in vacuo, extracted with ethyl acetate, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (DCM/MeOH 85/15) to give 0.4 g of title compound.

Step 4) (R)-*N*-(1-(1-Naphthyl)ethyl)-*N*-((4-(3-*N,N*-dimethylamino)propoxy-3-(4-methoxyphenyl)phenylmethyl)amine:

The title compound was prepared from 4-(3-*N,N*-dimethylamino)propoxy-3-(4-methoxyphenyl)benzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure B.



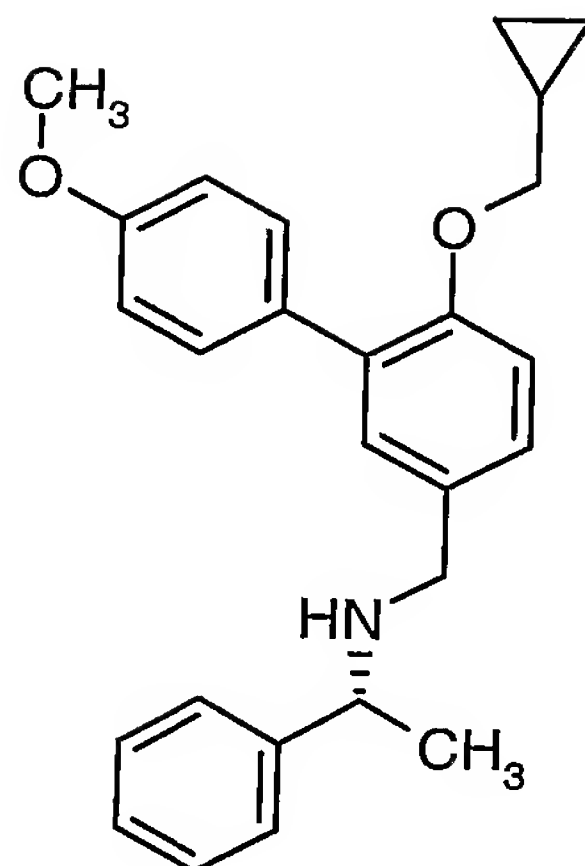
Mass (calculated): [468]; (found): [M+H<sup>+</sup>] = 469.

NMR (400 MHz, CDCl<sub>3</sub>): 1.45 (3H, d, *J* = 6 Hz, NCHCH<sub>3</sub>); 1.85-1.95 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N); 2.25 (6H, s, Me<sub>2</sub>N); 2.4-2.5 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N); ); 3.6 and 3.65 (2H, dd, *J* = 12 Hz, CH<sub>2</sub>N); 3.7 (3H, s, CH<sub>3</sub>O); 3.9 (2H, t, *J* = 6 Hz, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N); 4.65 (1H, q, *J* = 6 Hz, NCHCH<sub>3</sub>); 6.8-6.9 (3H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.3-7.5 (5H, m, aryl-H); 7.7 (2H, d, *J* = 8 Hz, aryl-H); 7.8-7.85 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

**Example 56**

(R)-*N*-(1-Phenylethyl)-*N*-((4-(cyclopropylmethoxy-3-(4-methoxyphenyl)-phenylmethyl)amine

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Step 1) 3-bromo-4-cyclopropylmethoxybenzaldehyde:

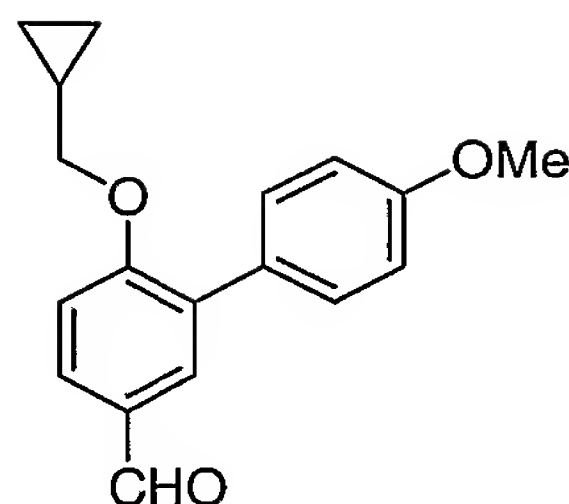
A suspension of 3-bromo-4-hydroxybenzaldehyde (5.03 g, 25 mmol),  
 5 bromomethylcyclopropane (28 mmol, 2.72 mL) and potassium carbonate (37.5  
 mmol, 5.14 g) in DMF (30 mL) was heated at 110 C for three days. The solid was  
 filtered off and the solvent was removed under reduced pressure, to give an orange  
 residue which was taken into ethyl acetate and washed with water and then  
 saturated brine. The organic phase was dried over  $\text{Mg}_2\text{SO}_4$  and solvent removed to  
 10 afford 5.56 g of the title material.

$\text{C}_{11}\text{H}_{11}\text{BrO}_2$  Mass (calculated): [255]; (found): 255, 257 and 296, 298 (M +  
 MeCN).

NMR (400 MHz,  $\text{CDCl}_3$ ): 0.15-0.2 (2H, m, cyclopropyl- $\text{CH}_2$ ); 0.4-0.5 (2H, m,  
 cyclopropyl- $\text{CH}_2$ ); 1-1.15 (1H, m, cyclopropyl-CH); 3.8 (2H, d,  $J=7$  Hz,  $\text{OCH}_2$ );  
 15 7.75 (1H, d,  $J=8$  Hz, aryl-H); 7.55 (1H, dd,  $J=2$  and 8 Hz, aryl-H); 7.9 (1H, d,  $J=$   
 2 Hz, aryl-H); 9.6 (1H, s, CHO).

Step 2) 4-Cyclopropylmethoxy-3-(4'-methoxyphenyl)benzenecarboxaldehyde:

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To a degassed solution of 3-bromo-4-cyclopropylmethoxybenzaldehyde (1.53 g, 6 mmol), 4-methoxybenzeneboronic acid (1.22 g, 8 mmol) and potassium carbonate (2.74 g, 20 mmol) in toluene/ethanol 2/1 (40 mL), Pd(PPh<sub>3</sub>)<sub>4</sub> (100 mg) was added and the mixture was degassed for further 5 minutes. The mixture was then refluxed for 12 hours. The solid is filtered off, and the solvent partitioned between ethyl acetate and water and extracted. The organic solvent was removed under reduced pressure, dried over sodium sulphate and purified by column chromatography on silica (hexane/ethyl acetate 8/2) to afford 1.52 g of product.

10 C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>

Mass (calculated): [282]; (found): [M+H<sup>+</sup>] = 283; LC Rt = 1.65, 97%.

NMR (400 MHz, CDCl<sub>3</sub>): 0.15-0.25 (2H, m, cyclopropyl-CH<sub>2</sub>); 0.45-0.55 (2H, m, cyclopropyl-CH<sub>2</sub>); 1.05-1.15 (1H, m, cyclopropyl-CH); 3.75 (3H, s, MeO); 3.8 (2H, d, *J* = 7 Hz, arylOCH<sub>2</sub>); 6.9 (2H, 2, *J* = 7 Hz, 8.5 Hz, aryl-H); 7.9 (1H, d, *J* = 8.5 Hz, aryl-H); 7.4 (2H, d, *J* = 8.5 Hz, aryl-H); 7.65 (1H, dd, *J* = 2 and 8.5 Hz, aryl-H); 7.75 (1H, d, *J* = 2 Hz, aryl-H); 9.8 (1H, s, CHO).

Step 3) (R)-N-(1-Phenylethyl)-N-((4-(cyclopropylmethoxy)-3-(4-methoxyphenyl)-phenylmethyl)amine:

20 The title compound was prepared from 4-cyclopropylmethoxy-3-(4'-methoxyphenyl)benzenecarboxaldehyde and (R)-α-methylbenzylamine according to general procedure A.

C<sub>26</sub>H<sub>29</sub>NO<sub>2</sub>

Mass (calculated): [387]; (found): [M+H<sup>+</sup>] = 267, 388.

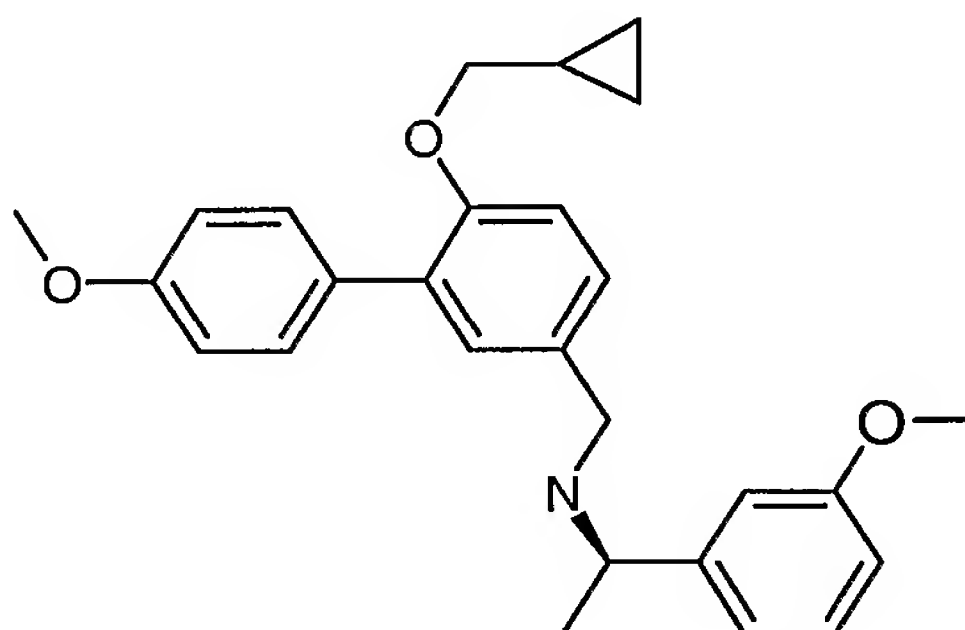
25 NMR (400 MHz, CDCl<sub>3</sub>): 0.2 (2H, m, cyclopropyl-H); 0.45 (2H, m, cyclopropyl-H); 1.15 (1H, m, cyclopropyl-H); 1.3 (3H, d, *J* = 6 Hz, NCHCH<sub>3</sub>); 3.5 and 3.55 (2H, dd, *J* = 12 Hz, CH<sub>2</sub>N); 3.7 (2H, d, *J* = 6 Hz, cyclopropylCH<sub>2</sub>O); 3.7-3.8 (4H, m, MeO and NCHMe); 6.8 (1H, d, *J* = 8 Hz, aryl-H); 6.85 (2H, d, *J* = 8 Hz, aryl-

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H); 7.1 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.15-7.25 (2H, m, aryl-H); 7.25-7.35 (4H, m, aryl-H); 7.45 (2H, d,  $J = 8$  Hz, aryl-H).

**Example 57**

5 (R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-cyclopropylmethoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



10 The title compound was prepared from 4-cyclopropylmethoxy-3-(4'-methoxyphenyl)benzenecarboxaldehyde and (R)-3-methoxy- $\alpha$ -methylbenzylamine according to general procedure A.

$C_{27}H_{31}NO_3$

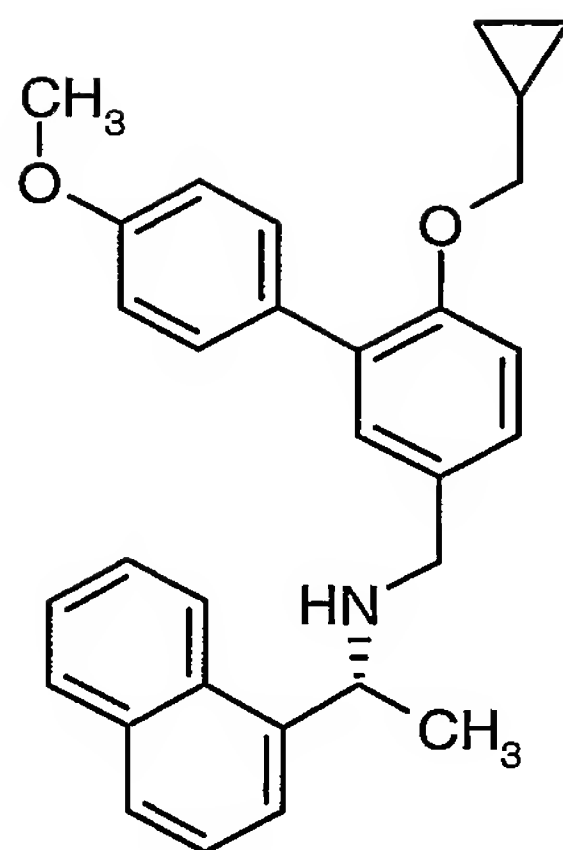
Mass (calculated): [417]; (found):  $[M+H^+] = 267, 418$ .

15 NMR (400 MHz,  $CDCl_3$ ): 0.2 (2H, m, cyclopropyl-H); 0.45 (2H, m, cyclopropyl-H); 1.1 (1H, m, cyclopropyl-H); 1.3 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.5 and 3.55 (2H, dd,  $J = 12$  Hz,  $CH_2N$ ); 3.65 (2H, d,  $J = 6$  Hz, cyclopropyl $CH_2O$ ); 3.7 (3H, s,  $CH_3O$ ); 3.75-3.85 (4H, m, MeO and  $NCHMe$ ); 6.75 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 6.8 (1H, d,  $J = 8$  Hz, aryl-H); 6.85-6.95 (4H, m, aryl-H); 7.1 (1H, dd,  $J = 1$  and 8 Hz, aryl-H); 7.15 (1H, d,  $J = 1$  Hz, aryl-H); 7.15-7.25 (1H, m, aryl-H); 7.45 (2H, d,  $J = 8$  Hz, aryl-H).

**Example 58**

25 (R)-N-(1-(1-Naphthyl)ethyl)-N-((4-(cyclopropylmethoxy-3-(4-methoxyphenyl)phenyl)methyl)amine

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The title compound was prepared from 4-cyclopropylmethoxy-3-(4'-methoxyphenyl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure A.

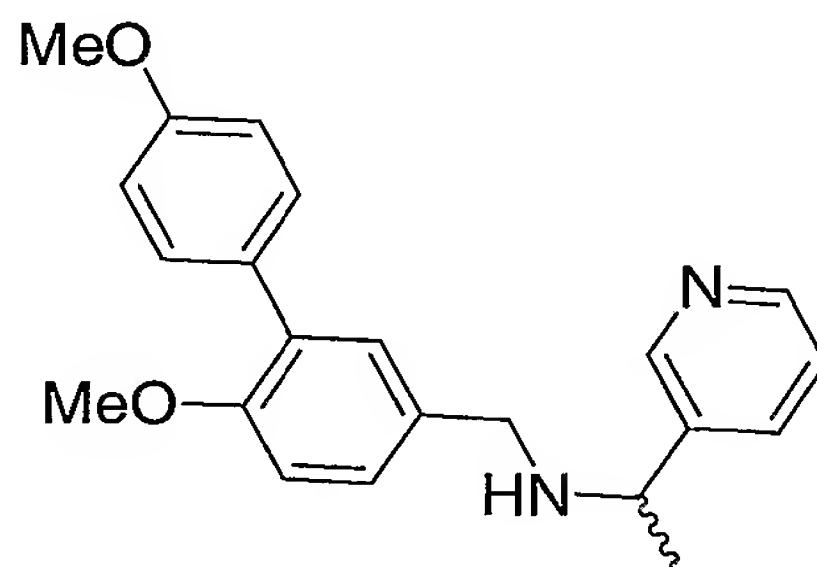
$C_{30}H_{31}NO_2$

Mass (calculated): [437]; (found):  $[M+H^+] = 438, 267, 875$ .

NMR (400 MHz,  $CDCl_3$ ): 0.2 (2H, m, cyclopropyl-H); 0.45 (2H, m, cyclopropyl-H); 1.15 (1H, m, cyclopropyl-H); 1.45 (3H, d,  $J = 6$  Hz,  $NCHCH_3$ ); 3.6 (1H, d,  $J = 12$  Hz,  $CH_2N$ ); 3.65-3.75 (3H, m,  $CH_2N$  and cyclopropyl $CH_2O$ ); 3.75 (3H, s, MeO); 4.65 (1H, q,  $J = 6$  Hz,  $NCHMe$ ); 6.75-6.9 (3H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.35-7.5 (5H, m, aryl-H); 7.65-7.5 (2H, m, aryl-H); 7.8-7.9 (1H, m, aryl-H); 8.0-8.1 (1H, m, aryl-H).

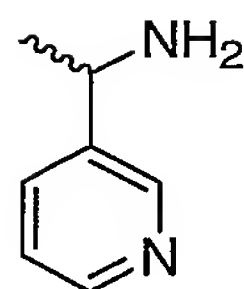
### Example 59

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-3-yl-ethyl)-amine



Step 1) 1-Pyridin-3-yl-ethylamine:

- 95 -



3-Acetylpyridine (2.4 g, 20 mmol, Aldrich) was dissolved in 2M ammonia solution in methyl alcohol (50 mL, 100 mmol, Aldrich) and acetic acid (15 mL, J.T. Baker) was slowly added at 0 C. After stirring for 3 h at room temperature, the sodium cyanoborohydride (5.0 g, 80 mmol, Aldrich) was added to the solution at 0 C. The mixture was stirred under nitrogen at room temperature for overnight then the reaction was cooled at ice bath and quenched with aqueous 5 N sodium hydroxide (30 mL, 150 mmol, J.T. Baker). The methyl alcohol was removed from the mixture via vacuo. The residue was extracted by diethyl ether (30 mL x 4). The combined organic phases were dried over anhydrous magnesium sulfate and concentrated via vacuo to give crude 1-pyridin-3-yl-ethylamine as light yellow oil in 44% yield (1.07 g, 8.8 mmol).



MS (ESI, pos. ion) m/z: 123.0 (M+1); MS (ESI, neg. ion) m/z: 121.0 (M-1).

Step 2) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-3-yl-ethyl)-amine:

1-Pyridin-3-yl-ethylamine (245 mg, 2 mmol) and 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (121 mg, 0.5 mmol) were dissolved in dichloroethane (10 mL). After stirring for 6 h at room temperature, the sodium triacetoxyborohydride (212 mg, 1.0 mmol, Aldrich) was added to the solution at 0 C. The mixture was stirred under nitrogen at room temperature for overnight then the reaction was cooled at ice bath and quenched with saturated aqueous sodium bicarbonate (10 mL). The organic phase was separated and the aqueous phase was extracted with dichloroethane (10 mL x 3). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo. The crude was purified by column chromatography (silica gel, ethyl acetate) to give the title compound as white solid in 50% yield (87 mg, 0.25 mmol).



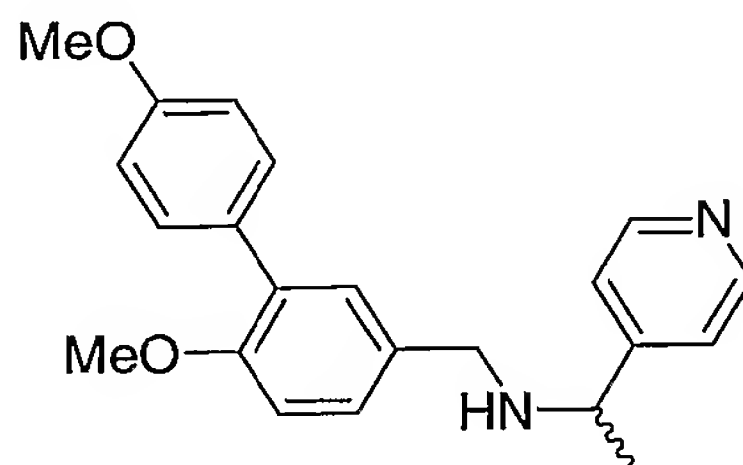
MS (ESI, pos. ion) m/z: 349.2 (M+1); MS (ESI, neg. ion) m/z: 347.2 (M-1).



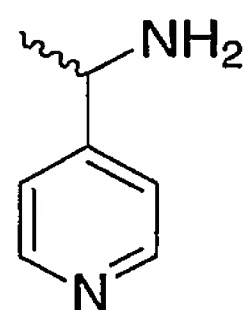
- 96 -

**Example 60**

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-4-yl-ethyl)-amine



5

Step 1) 1-Pyridin-4-yl-ethylamine:

10 The title compound was prepared by the same procedure for preparing 1-pyridin-3-yl-ethylamine from 4-acetylpyridine (2.4 g, 20 mmol, Aldrich), 2 M ammonia solution in methyl alcohol (50 mL, 100 mmol, Aldrich), acetic acid (15 mL, J.T. Baker) and sodium cyanoborohydride (5.0 g, 80 mmol, Aldrich). The title compound was obtained in form as light yellow oil in 51% yield (1.25 g, 10.2 mmol).

15



MS (ESI, pos. ion) m/z: 123.0 (M+1); MS (ESI, neg. ion) m/z: 121.0 (M-1).

Step 2) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-4-yl-ethyl)-amine:

20 The title compound was prepared by the same procedure for preparing (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-3-yl-ethyl)-amine from 1-Pyridin-4-yl-ethylamine (245 mg, 2 mmol), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (121 mg, 0.5 mmol) and sodium triacetoxyborohydride (212 mg, 1.0 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as white solid in 51% yield (89 mg, 0.26 mmol).

25

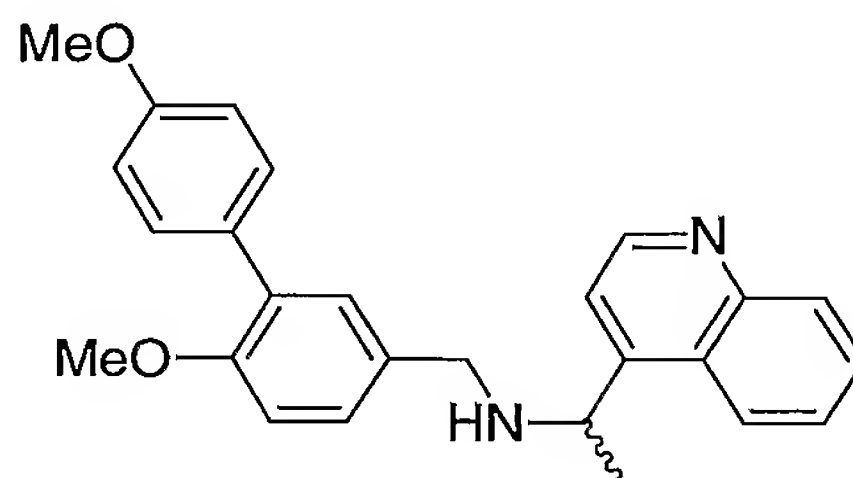
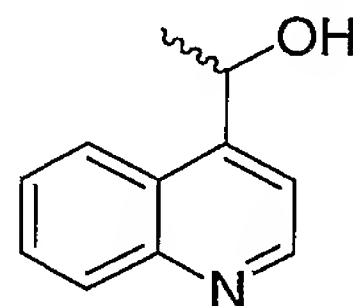


MS (ESI, pos. ion) m/z: 349.2 (M+1); MS (ESI, neg. ion) m/z: 347.2 (M-1).

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**Example 61****(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine**

5

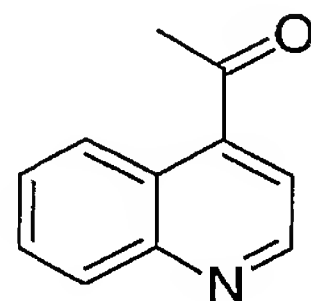
Step 1) 1-Quinolin-4-yl-ethanol:

10 4-Quinolinecarboxaldehyde (1.57 g, 10 mmol, Aldrich) was dissolved in anhydrous THF (30 mL) and cooled to  $-78^{\circ}\text{C}$ . The 3 M methyl magnesium iodide solution in diethyl ether (5 mL, 15 mmol, Aldrich) was slowly added to the reaction solution in dry ice bath. The reaction mixture was allowed to stir under nitrogen at room temperature for overnight then the reaction was cooled at ice

15 bath and quenched with saturated aqueous ammonium chloride (30 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (30 mL x 2). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo to give crude title compound as light yellow syrup in 100% yield (1.73 g, 10 mmol).

20  $\text{C}_{11}\text{H}_{11}\text{NO}$ 

MS (ESI, pos. ion) m/z: 174.4 (M+1); MS (ESI, neg. ion) m/z: 172.2 (M-1).

Step 2) 1-Quinolin-4-yl-ethanone:

25

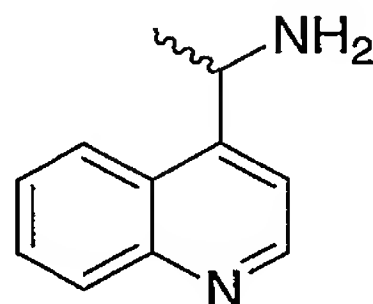
- 98 -

To the mixture of manganese oxide (8.69 g, 100 mmol, Aldrich) in dichloromethane (80 mL) was added 1-quinolin-4-yl-ethanol (1.73 g, 10 mmol). The reaction mixture was refluxed for overnight and then cooled to room temperature. The solid was filtered out through Celite pad. The organic solution  
5 dried over anhydrous magnesium sulfate and concentrated via vacuo to give crude title compound as light yellow solid in 100% yield (1.71 g, 10.0 mmol).

 $C_{11}H_9NO$ 

MS (ESI, pos. ion) m/z: 172.10 (M+1); MS (ESI, neg. ion) m/z: 170.0 (M-1).

10 Step 3) 1-Quinolin-4-yl-ethylamine:

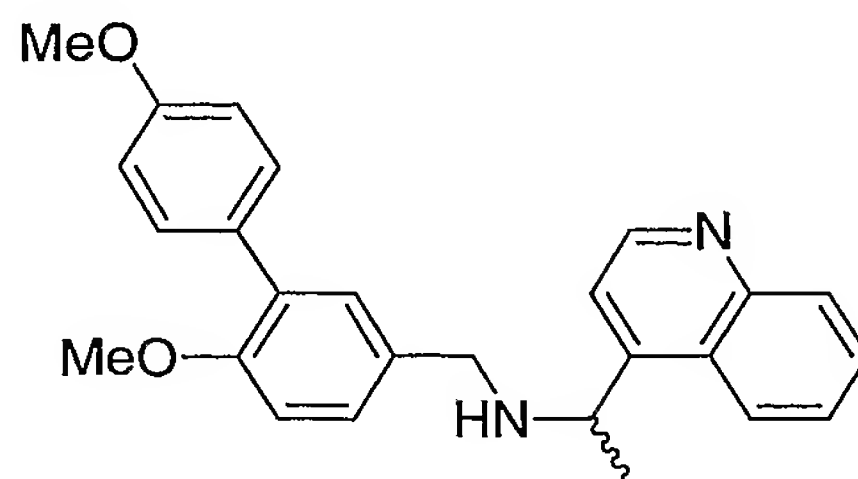


The title compound was prepared by the same procedure for preparing 1-pyridin-3-yl-ethylamine from 1-quinolin-4-yl-ethanone, (1.71 g, 10 mmol, Aldrich), 2 M ammonia solution in methyl alcohol, (40 mL, 80 mmol, Aldrich), acetic acid (10  
15 mL, J.T. Baker) and sodium cyanoborohydride (5.0 g, 80 mmol, Aldrich). The title compound obtained in form as light yellow solid in 100% yield (1.72 g, 10 mmol).

 $C_{11}H_{12}N_2$ 

20 MS (ESI, pos. ion) m/z: 173.0 (M+1); MS (ESI, neg. ion) m/z: 171.0 (M-1).

Step 4) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine:



25 The 1-quinolin-4-yl-ethylamine (510 mg, 3 mmol) and 6,4'-dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) were stirred with acetic acid (300 mg,

- 99 -

J.T.Baker) in methyl alcohol (15 mL) at room temperature for 4 h. To the reaction solution was added sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich) at 0°C. The mixture was stirred under nitrogen at room temperature for overnight then the reaction was cooled at ice bath and quenched with saturated aqueous sodium bicarbonate (30 mL). The methyl alcohol was removed from the mixture via vacuo. The residue was extracted by ethyl acetate (30 mL x 4). The combined organic phases were dried over anhydrous magnesium sulfate and concentrated via vacuo. The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as white solid in 72% yield (287 mg, 0.72 mmol).

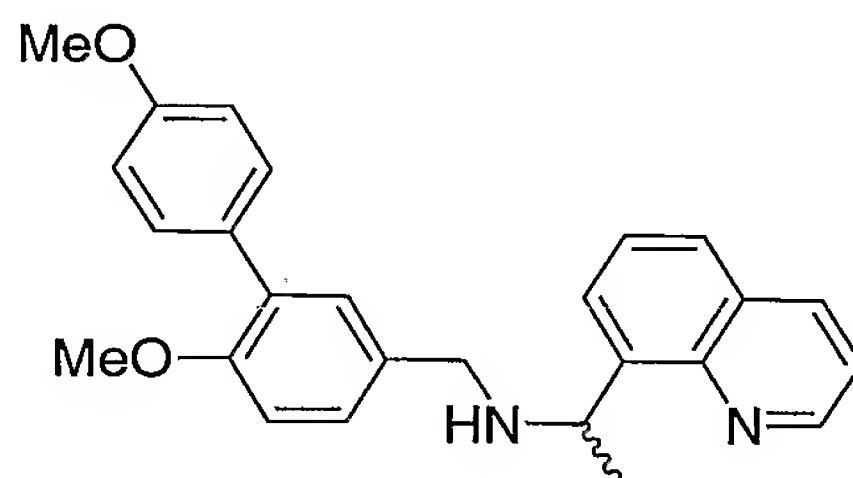
10  $C_{26}H_{26}N_2O_2$

MS (ESI, pos. ion) m/z: 399.2 (M+1); MS (ESI, neg. ion) m/z: 397.2 (M-1).

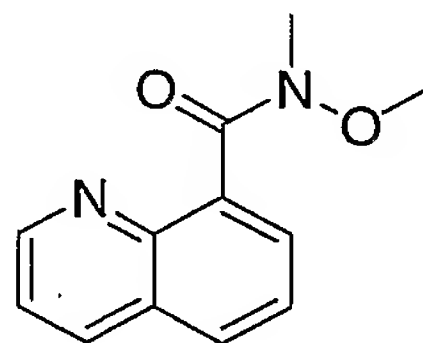
### Example 62

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-8-yl-ethyl)-amine

15



Step 1) Quinoline-8-carboxylic acid methoxy-methyl-amide:



20

To the solution of 1-isoquinolonecarboxylic acid (1.73 g, 10 mmol, Aldrich) in anhydrous N, N –dimethylformamide (30 mL) were added N, N-diisopropylethylamine (5.29 g, 40 mmol, Aldrich), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (7.6 g, 20 mmol, PerSeptive Biosystems GmbH), N,O-dimethylhydroxylamine hydrochloride (1.8 g, 20 mmol,

25

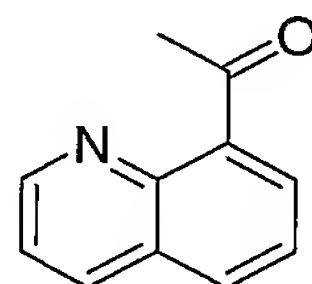
- 100 -

Aldrich) subsequently at room temperature. The reaction solution was allowed to stir for overnight at room temperature. The N, N –Dimethylformamide was removed via vacuo and the resulting residue was diluted in ethyl acetate (50 mL). After being washed by saturate aqueous sodium bicarbonate (50 mL) and  
5 brine (50 mL), the organic portion was dried over anhydrous magnesium sulfate and concentrated. The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as yellow syrup in 94% yield (2.04 g, 9.4 mmol).  
 $C_{12}H_{12}N_2O_2$

MS (ESI, pos. ion) m/z: 217.1 (M+1); MS (ESI, neg. ion) m/z: 215.0 (M-1).

10

Step 2) 1-Quinolin-8-yl-ethanone:



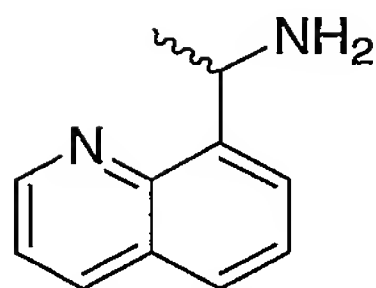
15 Quinoline-8-carboxylic acid methoxy-methyl-amide (2.16 g, 10 mmol) was dissolved in anhydrous THF (40 mL) and cooled to  $-78^{\circ}\text{C}$ . The 3 M methyl magnesium iodide solution in diethyl ether (4.0 mL, 12 mmol, Aldrich) was slowly added to the reaction solution in dry ice bath. The reaction mixture was allowed to stir under nitrogen at room temperature for overnight then the reaction  
20 was cooled at ice bath and quenched with saturated aqueous ammonium chloride (40 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (30 mL x 2). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo to give crude title compound as light yellow solid in 83% yield (1.42 g, 8.3 mmol).

25  $C_{11}H_9NO$

MS (ESI, pos. ion) m/z: 172.0 (M+1); MS (ESI, neg. ion) m/z: 170.1 (M-1).

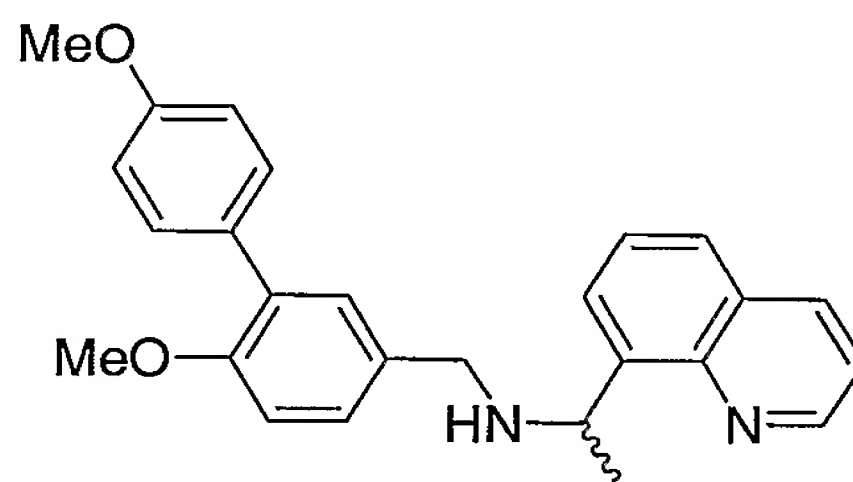
Step 3) 1-Quinolin-8-yl-ethylamine:

- 101 -



The title compound was prepared by the same procedure for preparing 1-pyridin-3-yl-ethan-1-amine from 1-quinolin-8-yl-ethanone (1.71 g, 10 mmol), 2 M ammonia solution in methyl alcohol, acetic acid (25 mL, 50 mmol, Aldrich) and sodium cyanoborohydride (2.5 g, 40 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as light yellow solid in 98% yield (1.68 g, 9.8 mmol). MS (ESI, pos. ion) m/z: 173.2 (M+1); MS (ESI, neg. ion) m/z: 171.0 (M-1).

Step 4) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-8-yl-ethyl)-amine:



The title compound was prepared by the same procedure for (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine from 1-quinolin-8-yl-ethanamine (510 mg, 3.0 mmol), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) and sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as white solid in 72% yield (287 mg, 0.72 mmol).

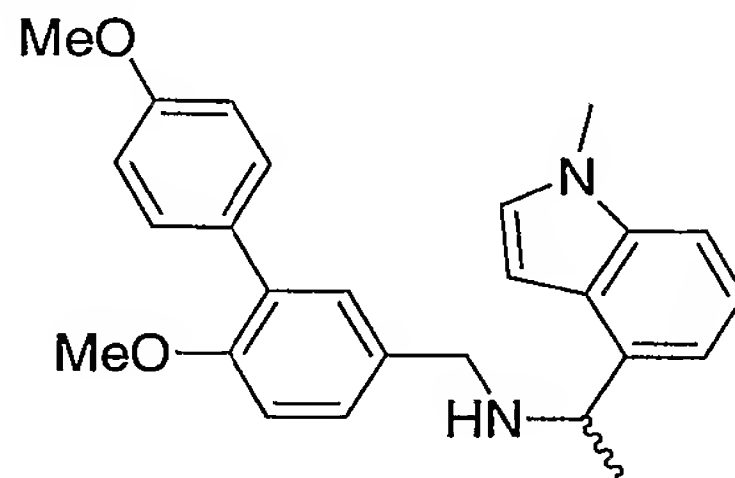
$C_{26}H_{26}N_2O_2$

MS (ESI, pos. ion) m/z: 399.2 (M+1); MS (ESI, neg. ion) m/z: 397.2 (M-1).

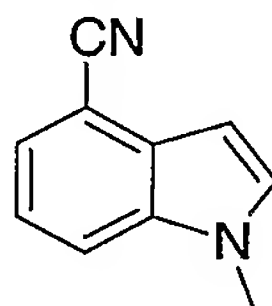
- 102 -

**Example 63**

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-[1-(1-methyl-1H-indol-4-yl)-ethyl]-amine



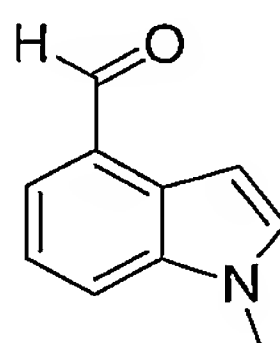
5

Step 1) 1-Methyl-1H-indole-4-carbonitrile:

4-Cyanoindole (2.8 g, 20 mmol, Biosynth International) was dissolved in N, N –  
 10 Dimethylformamide (25 mL). To the solution were added potassium carbonate  
 powder (5.5 g, 40 mmol, 325 mesh, Aldrich) and iodomethane (3.4 g, 24 mmol,  
 Aldrich). The mixture was stirred at room temperature for 48 h then the N, N –  
 Dimethylformamide was removed via vacuo and the residue was diluted in ethyl  
 15 acetate (100 mL). The organic solution was washed by water (50 mL), brine (50  
 mL). The resulting organic solution was dried over anhydrous magnesium sulfate  
 and concentrated via vacuo. The title compound was purified by column  
 chromatography (silica gel, hexane/ethyl acetate 3/2) in form as white solid in  
 97% yield (3.02 g, 19.4 mmol).



20 MS (ESI, pos. ion) m/z: 157.0 (M+1); MS (ESI, neg. ion) m/z: 155.0 (M-1).

Step 2) 1-Methyl-1H-indole-4-carbaldehyde:



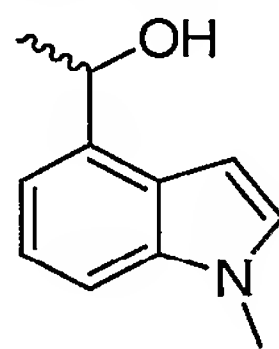
- 103 -

1-Methyl-1H-indole-4-carbonitrile (3.02 g, 19 mmol) was dissolved in anhydrous dichloromethane (30 mL) and the solution was cooled to  $-78^{\circ}\text{C}$ . To the reaction solution was slowly added 1.5 M diisobutylaluminum hydride in toluene (12.6 mL, 19 mmol, Aldrich). The reaction mixture was allowed to stir under nitrogen at room temperature for 6 h then it was cooled again in ice bath and quenched with methyl alcohol (4 mL). The resulting solution was poured to 15% aqueous sulfuric acid solution (40 mL) at  $0^{\circ}\text{C}$ . After stirring vigorously for 1 h, the mixture was added aqueous 5 N sodium hydroxide to adjust  $\text{PH} > 12$ . The organic phase was separated and the aqueous phase was extracted with ethyl acetate (40 mL x 3). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo. The title compound was purified by column chromatography (silica gel, hexane/ethyl acetate 2/3) in form as light yellow oil in 92% yield (2.8 g, 17.6 mmol).

$\text{C}_{10}\text{H}_9\text{NO}$

MS (ESI, pos. ion)  $m/z$ : 160.1 (M+1); MS (ESI, neg. ion)  $m/z$ : 158.0 (M-1).

Step 3) 1-(1-Methyl-1H-indol-4-yl)-ethanol:



20

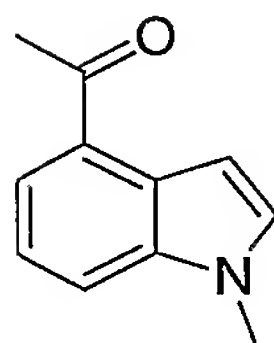
The title compound was prepared by the same procedure for 1-quinolin-4-yl-ethanol from 1-methyl-1H-indole-4-carbaldehyde (2.8 g, 17.6 mmol), 3 M methyl magnesium iodide solution in diethyl ether (10 mL, 30 mmol, Aldrich) and anhydrous tetrahydrofuran (20 mL). The crude title compound obtained in form as yellow oil in 97% yield (3.0 g, 17.1 mmol).

$\text{C}_{11}\text{H}_{13}\text{NO}$

MS (ESI, pos. ion)  $m/z$ : 176.0 (M+1); MS (ESI, neg. ion)  $m/z$ : 174.0 (M-1).

Step 4) 1-(1-Methyl-1H-indol-4-yl)-ethanone:

- 104 -

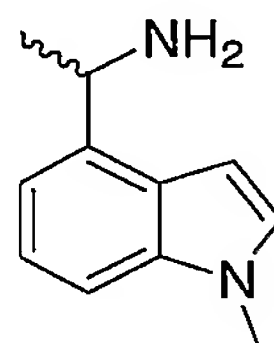


The title compound was prepared by the same procedure for 1-quinolin-4-yl-ethanone from 1-(1-Methyl-1H-indol-4-yl)-ethanol (3.0 g, 17 mmol), manganese oxide (8.69 g, 100 mmol, Aldrich) and dichloromethane (50 mL). The crude title compound was obtained in form as yellow oil in 98% yield (2.9 g, 16.7 mmol).

$C_{11}H_{11}NO$

MS (ESI, pos. ion) m/z: 174.0 (M+1); MS (ESI, neg. ion) m/z: 172.0 (M-1).

10 Step 5) 1-(1-Methyl-1H-indol-4-yl)-ethylamine:



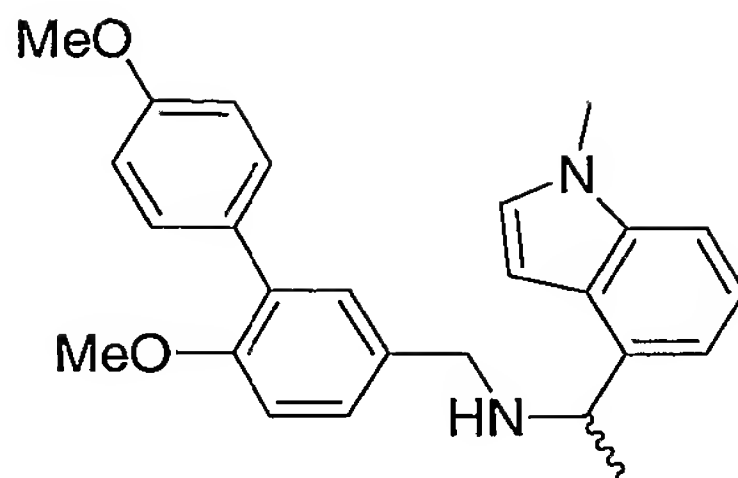
The title compound was prepared by the same procedure for preparing 1-pyridin-3-yl-ethylamine from 1-(1-methyl-1H-indol-4-yl)-ethanone (1.75 g, 10 mmol), 2 M ammonia solution in methyl alcohol (25 mL, 50 mmol, Aldrich), acetic acid (15 mL, J.T. Baker) and sodium cyanoborohydride (2.5 g, 40 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, 2 M ammonia solution in methyl alcohol/ethyl acetate 1/10) in form as light yellow oil in 48% yield (0.83 g, 4.8 mmol).

20  $C_{11}H_{14}N_2$

MS (ESI, pos. ion) m/z: 175.0 (M+1); MS (ESI, neg. ion) m/z: 173.0 (M-1).

Step 6) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-[1-(1-methyl-1H-indol-4-yl)-ethyl]-amine:

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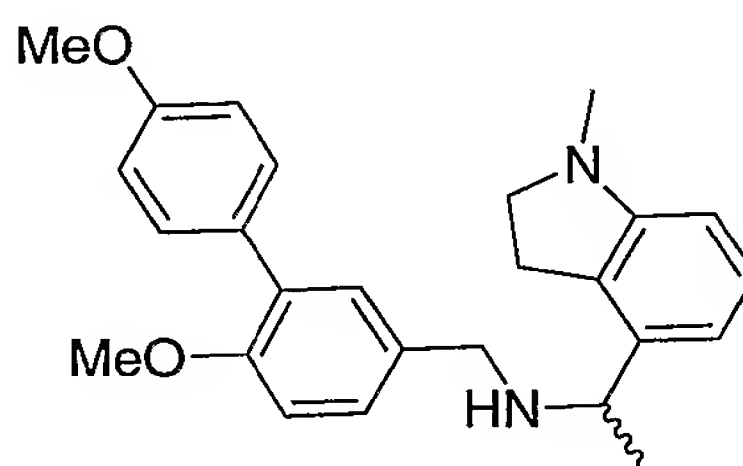
The title compound was prepared by the same procedure for (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine from 1-(1-Methyl-1H-indol-4-yl)-ethylamine (522 mg, 3.0 mmol), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) and sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, hexane/ethyl acetate 3/2) in form as white solid in 74% yield (296 mg, 0.74 mmol).



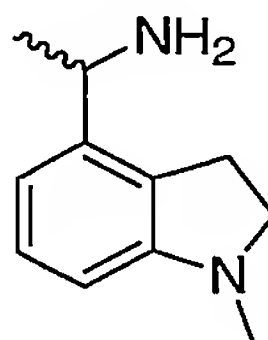
MS (ESI, pos. ion) m/z: 401.6 (M+1); MS (ESI, neg. ion) m/z: 399.2 (M-1).

#### Example 64

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-[1-(1-methyl-2,3-dihydro-1H-indol-4-yl)-ethyl]-amine



Step 1) 1-(1-Methyl-2,3-dihydro-1H-indol-4-yl)-ethylamine:



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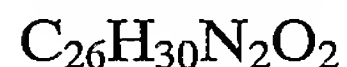
To the solution of 1-(1-Methyl-1H-indol-4-yl)-ethylamine (1.74 g, 10 mmol) with acetic acid (10 mL, J.T. Baker) was added sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich) at 0 C. The reaction mixture was stirred at room temperature for 4 h then quenched with saturate aqueous sodium bicarbonate (40 mL). The aqueous phase was extracted with ethyl acetate (30 mL x 4). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo. The title crude compound was obtained in form as light yellow oil in 78% yield (1.37, 7.8 mmol).



MS (ESI, pos. ion) m/z: 177.2 (M+1); MS (ESI, neg. ion) m/z: 175.0 (M-1).

Step 2) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-[1-(1-methyl-2,3-dihydro-1H-indol-4-yl)-ethyl]-amine:

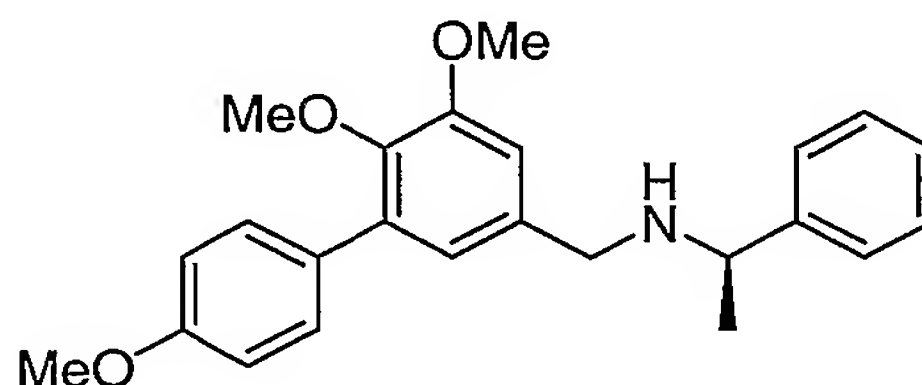
The title compound was prepared by the same procedure for (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine from 1-(1-Methyl-2,3-dihydro-1H-indol-4-yl)-ethylamine (528 mg, 3.0 mmol), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) and sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as white solid in 55% yield (221 mg, 5.5 mmol).



MS (ESI, pos. ion) m/z: 403.3 (M+1); MS (ESI, neg. ion) m/z: 401.4 (M-1).

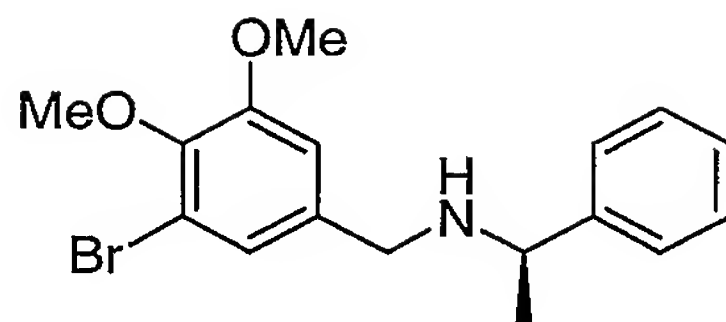
### Example 65

((1R)-1-Phenylethyl){[4,5-dimethoxy-3-(4-methoxyphenyl)phenyl]methyl}amine



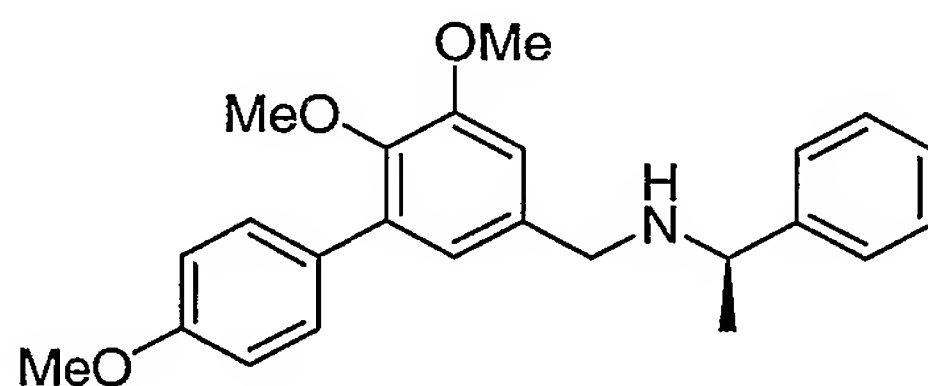
Step 1) ((1R)-1-Phenylethyl)[(3-bromo-4,5-dimethoxyphenyl)methyl]amine:

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To a solution of 3-bromo-4,5-dimethoxybenzaldehyde (5 g, 0.020 mol, Aldrich), (R)- $\alpha$ -methylbenzylamine (2.6 mL, 0.020 mol) and AcOH (5 mL) in 70 mL of MeOH was stirred at RT for 2 hours. The reaction solution was then cooled to 0 C and NaBH<sub>3</sub>CN (2.51 g, 0.040 mol) was added. The reaction was warmed up to RT in 2 hours and continued to stir for 16 hours. The reaction solution was concentrated *in vacuo* and the residue was re-dissolved in 150 mL of EtOAc. The organic solution was washed with 50 mL of saturated NaHCO<sub>3</sub> aqueous solution, followed by 50 mL of brine. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by a silica gel column chromatography (50% EtOAc in hexane) to provide white waxy solid (5.1 g).  
 $C_{17}H_{20}BrNO_2$   
 MS (ESI, pos. ion) m/z: 350.2 (M+1).

Step 2) ((1R)-1-Phenylethyl){[4,5-dimethoxy-3-(4-methoxyphenyl)phenyl]methyl}amine:



To a mixture of ((1R)-1-phenylethyl)[(3-bromo-4,5-dimethoxyphenyl)-methyl]amine (1.1 g, 3.15 mmol), 4-methoxyphenylboronic acid (0.479 g, 3.15 mmol), 2M Na<sub>2</sub>CO<sub>3</sub> (5 mL). 4 mL of EtOH in 10 mL of toluene was added 83 mg of PPh<sub>3</sub> (0.315 mmol) and 0.364 g of Pd (PPh<sub>3</sub>)<sub>4</sub> (0.315 mmol). The mixture was then heated to 80 C under N<sub>2</sub> for 16 hours. The mixture was cooled to RT and was diluted with 50 mL of EtOAc and 20 mL of sat. NaHCO<sub>3</sub> aq. solution. The

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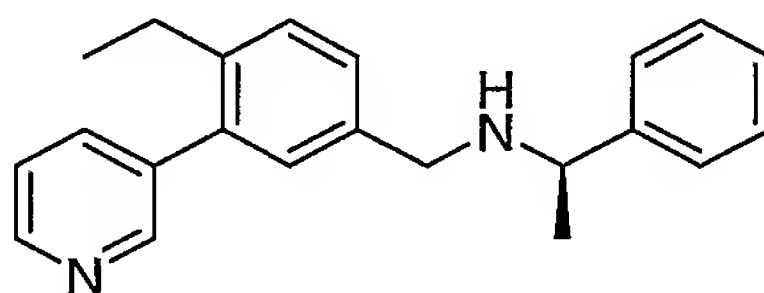
organic phase was washed with 30 mL of brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The light yellow oil was chromatographed (silica gel, 10% to 50% EtOAc in hexane) to provide light yellow oil (0.5 g). The product was treated with 1N HCl in Et<sub>2</sub>O to afford the HCl salt, which was re-crystallized in EtOAc to afford light yellow solid (0.5 g).

C<sub>24</sub>H<sub>27</sub>BNO<sub>3</sub>

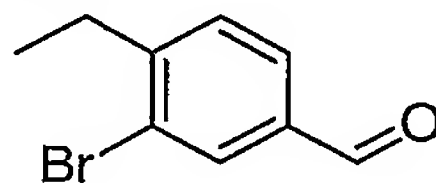
MS (ESI, pos. ion) m/z: 378.4 (M+1).

### Example 66

((1R)-1-Phenylethyl)[(4-ethyl-3-(3-pyridyl)phenyl)methyl]amine



Step 1) 3-Bromo-4-ethylbenzaldehyde



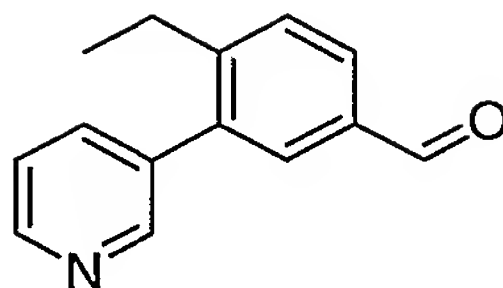
To a solution of 4-ethylbenzaldehyde (10 g, 0.0745mol, Aldrich) in TFA/98% H<sub>2</sub>SO<sub>4</sub> (4/1, 125 mL) mixture was added NBS (13.26 g, 0.0745 mol, Aldrich) at RT and continued to stir for 16 hours. The solvent was then removed *in vacuo* and the residue was dissolved in 200 mL of EtOAc. 1N NaOH solution (about 150 mL) was added to the solution and the organic phase was separated, washed with 100 mL of brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The oily residue was chromatographed (silica gel, 50% EtOAc in hexane) to afford orange oil as desired product (11.55 g).

C<sub>9</sub>H<sub>9</sub>BrO

MS (ESI, pos. ion) m/z: 227.0 (M+15).

Step 2) 4-Ethyl-3-(3-pyridyl)benzaldehyde:

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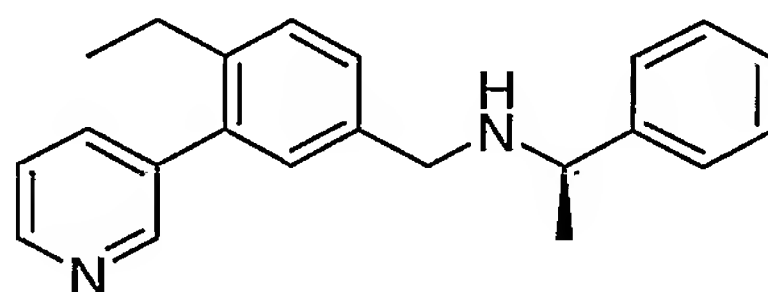


To a mixture of 3-bromo-4-ethylbenzaldehyde (2.45 g, 0.0115 mol), pyridine 3-boronic acid (1.42 g, 0.0115 mol, Matrix Scientific), 2M Na<sub>2</sub>CO<sub>3</sub> (15 mL) in 30 mL of toluene was added 1.33 g of Pd (PPh<sub>3</sub>)<sub>4</sub> (1.15 mmol, Aldrich). The mixture was then heated to 80 C under N<sub>2</sub> for 16 hours. The mixture was cooled to RT and was diluted with 100 mL of EtOAc and 40 mL of sat. NaHCO<sub>3</sub> aq. solution. The organic phase was washed with 40 mL of brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was chromatographed (silica gel, 20% EtOAc in hexane) to provide yellow oil (1.2 g).

10 C<sub>14</sub>H<sub>13</sub>NO

MS (ESI, pos. ion) m/z: 212.4 (M+1).

Step 3) ((1R)-1-Phenylethyl)[(4-ethyl-3-(3-pyridyl)phenyl)methyl]amine:



15

A solution of 4-ethyl-3-(3-pyridyl)benzaldehyde (0.2 g, 0.95 mmol), (R)- $\alpha$ -methylbenzylamine (0.121 mL, 0.95 mmol) and AcOH (1 mL) in 10 mL of MeOH was stirred at RT for 3 hours. The reaction solution was then cooled to 0 C and NaBH<sub>3</sub>CN (0.18 g, 2.85 mmol) was added. The reaction was warmed up to RT continued to stir 3 hours. The reaction solution was concentrated *in vacuo* and the residue was re-dissolved in 50 mL of EtOAc. The organic solution was washed with 20 mL of saturated NaHCO<sub>3</sub> aqueous solution, followed by 20 mL of brine. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by a silica gel column chromatography (20% of EtOAc in hexane) to provide colorless oil (0.2 g). The product was treated with 1N HCl in Et<sub>2</sub>O and the HCl salt was re-crystallized in MeOH/Et<sub>2</sub>O (1:10) mixture to provide white solid (0.2 g).

20  
25



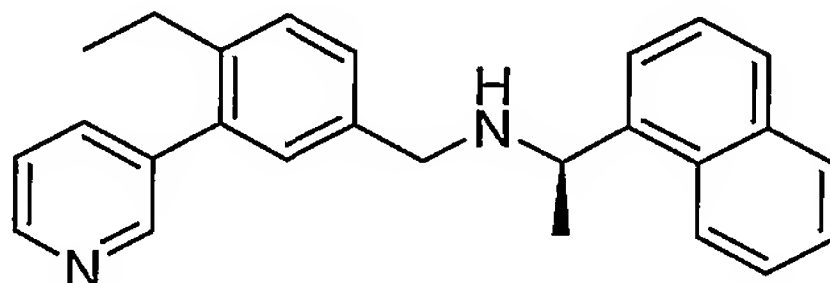
- 110 -

 $C_{22}H_{24}N_2$ 

MS (ESI, pos. ion) m/z: 317.3 (M+1).

**Example 67**

5 ((1R)-1-Naphthylethyl)[(4-ethyl-3-(3-pyridyl)phenyl)methyl]amine



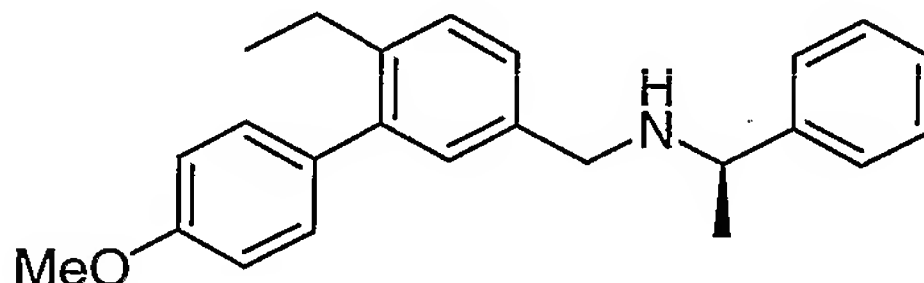
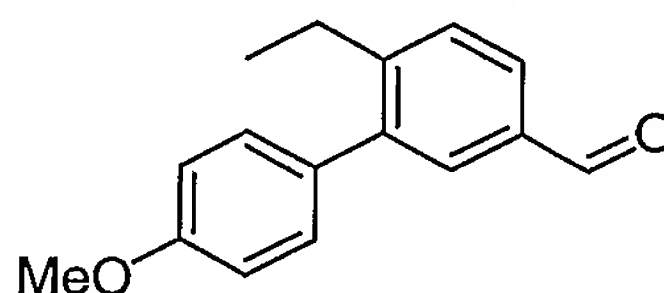
The title compound (0.22 g, white solid as HCl salt) was prepared from 4-ethyl-3-(3-pyridyl)benzaldehyde (0.22 g) and (R)-1-(1-naphthyl)ethylamine (0.17 mL) analogously to Example 66, step 3.

 $C_{26}H_{26}N_2$ 

MS (ESI, pos. ion) m/z: 367.3 (M+1).

**Example 68**

15 ((1R)-1-phenylethyl){[4-ethyl-3-(4-methoxyphenyl)phenyl)methyl]amine

20 Step 1) 4-Ethyl-3-(4-methoxyphenyl)benzaldehyde:

To a mixture of 3-bromo-4-ethylbenzaldehyde (1.5 g, 7.07 mmol), 4-methoxyphenylboronic acid (1.075 g, 7.07 mmol), 2M  $Na_2CO_3$  (10 mL) in 20 mL of toluene was added 0.817 g of Pd ( $PPh_3$ )<sub>4</sub> (0.707 mmol). The mixture was then heated to 80 C under  $N_2$  for 16 hours. The mixture was cooled to RT and was diluted with 100 mL of EtOAc and 50 mL of sat.  $NaHCO_3$  aq. solution. The

- 111 -

organic phase was washed with 40 mL of brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was chromatographed (silica gel, 10% EtOAc in hexane) to provide light yellow solid (2.1 g).

C<sub>16</sub>H<sub>16</sub>O<sub>2</sub>

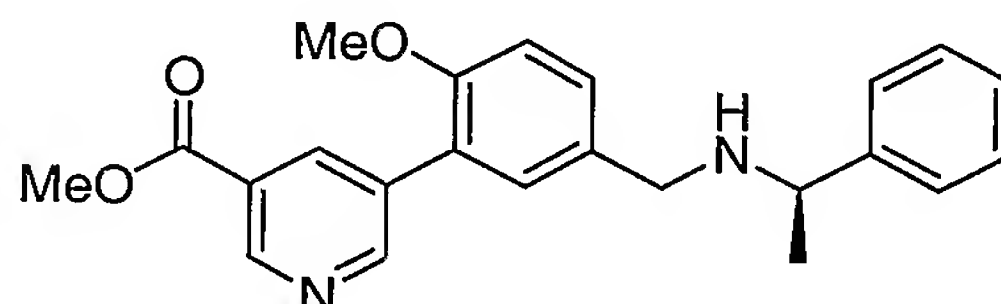
5 MS (ESI, pos. ion) m/z: 241.1 (M+1).

Step 2) ((1R)-1-phenylethyl){[4-ethyl-3-(4-methoxyphenyl)phenyl]methyl}amine:

The title compound (0.2 g, white solid as HCl salt) was prepared from 4-ethyl-3-(4-methoxyphenyl)benzaldehyde (0.5 g) and (R)- $\alpha$ -methylbenzylamine (0.265 mL) analogously to Example 66, step 3.

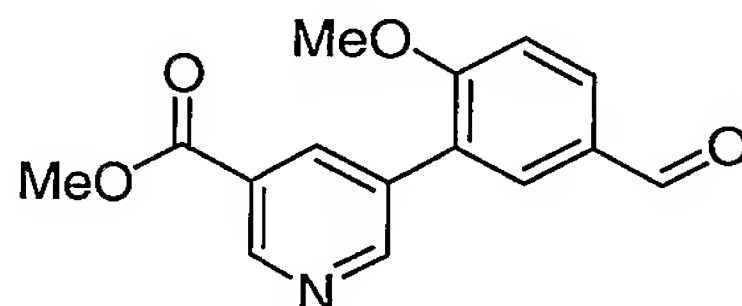
### Example 69

15 Methyl 5-(5-{[((1R)-1-phenylethyl)amino]methyl}-2-methoxyphenyl)pyridine-3-carboxylate



20

Step 1) Methyl 5-(3-formyl-6-methoxyphenyl)pyridine-3-carboxylate:



To a mixture of 5-bromonicotinate (2.16 g, 0.01 mol, Avocado Research) and (5-formyl-2-methoxyphenyl)boronic acid (1.79 g, 0.01 mol, Matrix Scientific), 2M Na<sub>2</sub>CO<sub>3</sub> (10 mL) in 20 mL of toluene was added 1.15 g of Pd(PPh<sub>3</sub>)<sub>4</sub> (1.0 mmol). The mixture was then heated to 80 C under N<sub>2</sub> for 16 hours. The mixture was cooled to RT and was diluted with 100 mL of EtOAc and 50 mL of sat. NaHCO<sub>3</sub>

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aq. solution. The organic phase was washed with 40 mL of brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The crude product was chromatographed (silica gel, 50% EtOAc in hexane) to provide white solid (1.2 g).

$\text{C}_{15}\text{H}_{13}\text{NO}_4$

5 MS (ESI, pos. ion)  $m/z$ : 272.3 (M+1).

Step 2) Methyl 5-(5-{[[(1R)-1-phenylethyl]amino]methyl}-2-methoxyphenyl)pyridine-3-carboxylate:

The title compound (0.4 g, white solid as HCl salt) was prepared from 4-ethyl-3-(4-methoxyphenyl)benzaldehyde (0.5 g) and (R)- $\alpha$ -methylbenzylamine (0.265 mL) analogously to Example 66, step 3.

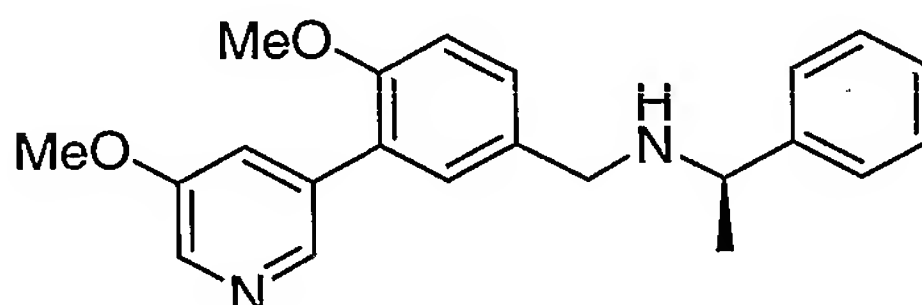
$\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_3$

MS (ESI, pos. ion)  $m/z$ : 377.5 (M+1).

15

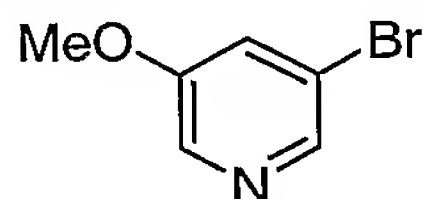
**Example 70**

((1R)-1-Phenylethyl){[4-methoxy-3-(5-methoxy(3-pyridyl))phenyl]methyl}amine



20

Step 1) 3-Bromo-5-methoxypyridine:



1.45 g of Na (0.063 mol) were added to 100 mL of MeOH and the resulted solution was stirred at RT for 30 minutes. The solution was then concentrated at 65 C *in vacuo* for 40 minutes. The white solid obtained was dissolved in 100 mL of DMF. 15 g of 3,5-dibromopyridine (0.063 mol) were added and the reaction was heated to 65 C for 16 hours. The reaction was cooled to RT and diluted with 200 mL of EtOAc and 100 mL of sat. aq.  $\text{NaHCO}_3$  solution. The organic phase

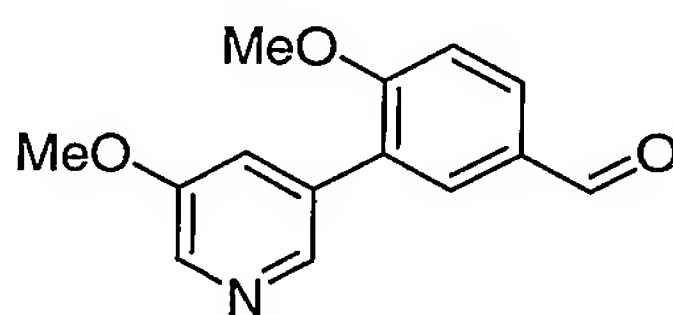
- 113 -

was separated and was washed with 100 mL of brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The crude product was chromatographed (silica gel, 10% EtOAc in hexane) to provide colorless crystals (10 g).

$\text{C}_6\text{H}_6\text{BrNO}$

5 MS (ESI, pos. ion)  $m/z$ : 188.1 (M+1).

Step 2) 4-Methoxy-3-(5-methoxy(3-pyridyl))benzaldehyde:



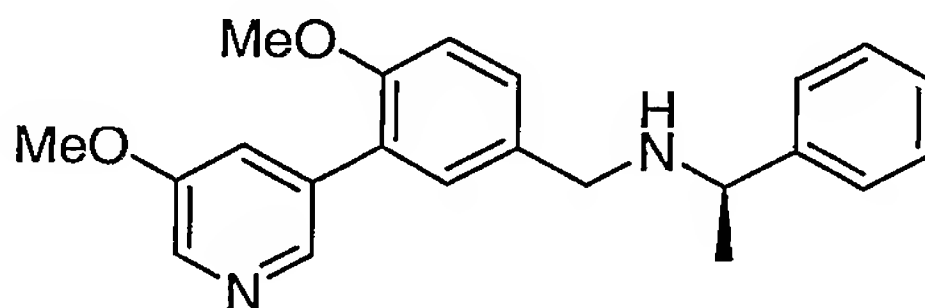
10 The title compound (2.5 g, white solid) was prepared from 3-Bromo-5-methoxypyridine (2.17 g, 0.0116 mol) and (5-formyl-2-methoxyphenyl)boronic acid (2.5 g, 0.014 mol, Matrix Scientific) analogously to Example 69, step 1.

$\text{C}_{14}\text{H}_{13}\text{NO}_3$

MS (ESI, pos. ion)  $m/z$ : 244.4 (M+1).

15

Step 3) ((1R)-1-Phenylethyl){[4-methoxy-3-(5-methoxy(3-pyridyl))phenyl]methyl}amine:



20 The title compound (0.8 g, white solid as HCl salt) was prepared from 4-methoxy-3-(5-methoxy(3-pyridyl))benzaldehyde (0.71 g) and (R)- $\alpha$ -methylbenzylamine (0.371 mL) analogously to Example 66, step 3.

$\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$

MS (ESI, pos. ion)  $m/z$ : 349.4 (M+1).

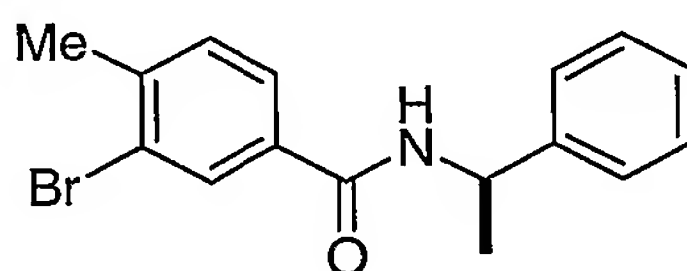
25

### Example 71

((1R)-1-Phenylethyl){[3-(4-methoxyphenyl)-4-methylphenyl]methyl}amine  
and

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## 4-(5-{[((1R)-1-Phenylethyl)amino]methyl}-2-methylphenyl)phenol

Step 1) N-((1R)-1-Phenylethyl)(3-bromo-4-methylphenyl)carboxamide:

5

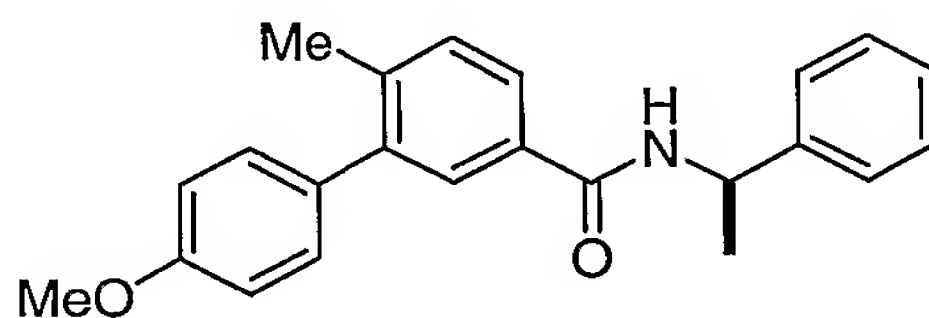
To a solution of 3-bromo-4-methylbenzoic acid (5.0 g, 0.023 mol) in CH<sub>2</sub>CH<sub>2</sub> (100 mL) was added oxalyl chloride (8.67 g, 0.069 mol). After 10 minutes, 1.0 mL of DMF was added slowly and the mixture was continued to stir at RT for 2 hours. The volatile was removed *in vacuo*. The residue was re-dissolved in CH<sub>2</sub>CH<sub>2</sub> (100 mL) and transferred to a 125 mL additional funnel.

To a 500 mL Erlenmeyer flask equipped with a stir bar was added 100 mL of sat. aq. NaHCO<sub>3</sub> solution followed by 2.79 g of (R)- $\alpha$ -methylbenzylamine (0.023 mol) in 100 mL of CH<sub>2</sub>CH<sub>2</sub>. 3-Bromo-4-methylbenzoyl chloride in CH<sub>2</sub>Cl<sub>2</sub> (from above) was added dropwise to the Erlenmeyer flask and the reaction mixture was continued to stir at RT for 16 hours. The organic phase was diluted with 50 mL of CH<sub>2</sub>CH<sub>2</sub>, separated from aqueous phase, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was washed with 50 mL of Et<sub>2</sub>O and dried in an oven at 40 C overnight to afford light yellow solid (7.0 g, 0.022 mol, 96%).

15

C<sub>16</sub>H<sub>16</sub>BrNO

20 MS (ESI, pos. ion) m/z: 316.1 (M+1).

Step 2) N-((1R)-1-Phenylethyl)[3-(4-methoxyphenyl)-4-methylphenyl]carboxamide:

25 To a mixture of N-((1R)-1-phenylethyl)(3-bromo-4-methylphenyl)carboxamide (1.38 g, 4.32 mmol) and 4-methoxyphenylboronic acid (0.53 g, 4.32 mmol) in 10 mL of 2M Na<sub>2</sub>CO<sub>3</sub> aq. soln and 20 mL of toluene was bubbled through N<sub>2</sub> for 5 min. Catalyst Pd(PPh<sub>3</sub>)<sub>4</sub> (0.36 g, 0.314 mmol) was then added and the mixture

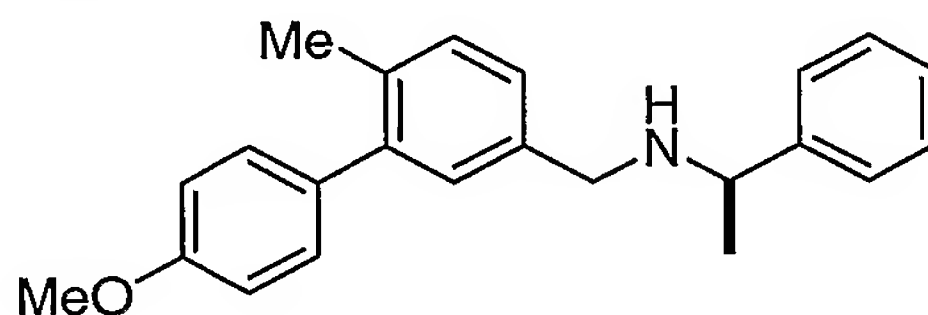
- 115 -

was heated to 80 C for 19 hours under N<sub>2</sub>. The reaction mixture was cooled to RT and was diluted with 100 mL of EtOAc and 50 mL of water. The organic layer was separated and washed with 50 mL of brine, and dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CHCl<sub>3</sub> to EtOAc) to provide yellow solid (1.0 g, 2.9 mmol, 92%).

C<sub>23</sub>H<sub>23</sub>NO<sub>2</sub>

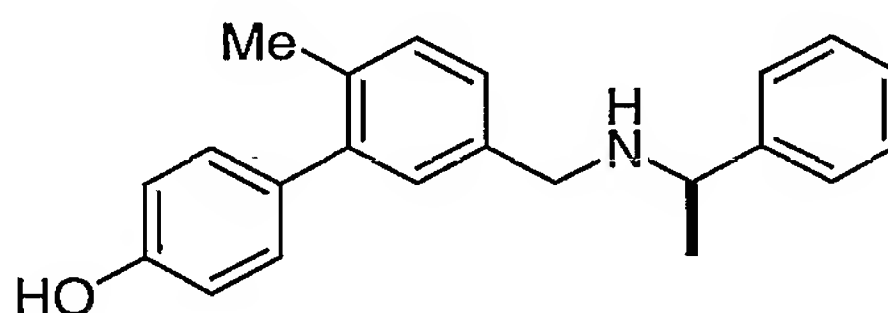
MS (ESI, pos. ion) m/z: 346.3 (M+1).

10 Step 3) ((1R)-1-Phenylethyl){[3-(4-methoxyphenyl)-4-methylphenyl]methyl}amine



and

4-(5-{[(((1R)-1-Phenylethyl)amino]methyl})-2-methylphenyl}phenol



15

To a solution of N-((1R)-1-phenylethyl)[3-(4-methoxyphenyl)-4-methylphenyl]carboxamide (0.12 g, 0.34 mmol) in 10mL of toluene was added DIBAL-H (1mL, 1.5mmol). The reaction was then heated to 100 C for 16 hours and cooled to RT. The reaction was quenched with 5 mL of 2N NaOH aq. soln. 100 mL of CH<sub>2</sub>Cl<sub>2</sub> was used to extract the product. The organic phase was washed with 30 mL of brine, dried over Na<sub>2</sub>SO<sub>3</sub> and concentrated *in vacuo*. The desired products were separated by silica gel column chromatography (30% to 60% EtOAc in hexane) provide ((1R)-1-phenylethyl){[3-(4-methoxyphenyl)-4-methylphenyl]methyl}amine and 4-(5-{[(((1R)-1-phenylethyl)amino]methyl})-2-methylphenyl}phenol, which were treated with 1N HCl in Et<sub>2</sub>O separately to provide the HCl salts as white solids.

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((1R)-1-Phenylethyl){[3-(4-methoxyphenyl)-4-methylphenyl]methyl}amine

$C_{23}H_{25}NO$

MS (ESI, pos. ion) m/z: 332.3 (M+1).

4-(5-{[((1R)-1-Phenylethyl)amino]methyl}-2-methylphenyl)phenol

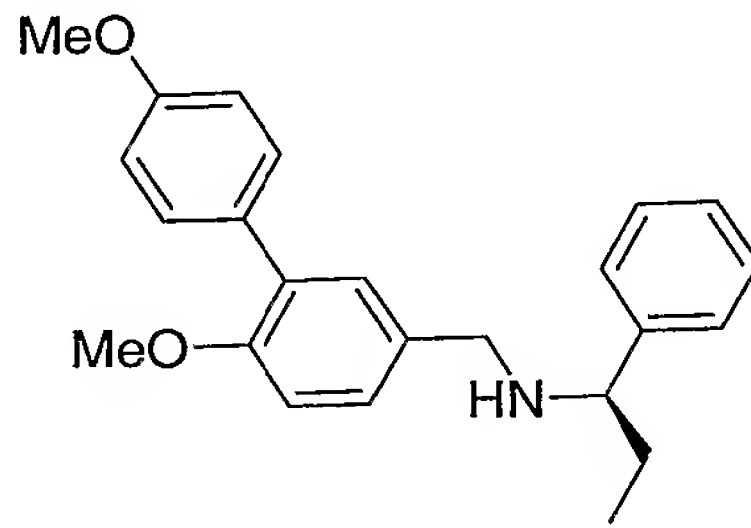
5  $C_{22}H_{23}NO$

MS (ESI, pos. ion) m/z: 318.2 (M+1); MS (ESI, neg. ion) m/z: 316.2 (M-1).

### Example 72

((1R)-1-Phenylpropyl){[4-methoxy-3-(4-methoxyphenyl)phenyl]methyl}amine

10



The title compound was prepared by the same procedure for (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine from (R)-(+)-1-phenyl-propylamine (405 mg, 3.0 mmol, Lancaster Synthesis Ltd.), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) and sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, hexane/ethyl acetate 2/3) in form as white solid in 52% yield (187 mg, 0.52 mmol).

20  $C_{24}H_{27}NO_2$

MS (ESI, pos. ion) m/z: 362.4 (M+1); MS (ESI, neg. ion) m/z: 360.3 (M-1).

The final products disclosed in Examples 73 to 109 were prepared according to Method C described earlier.

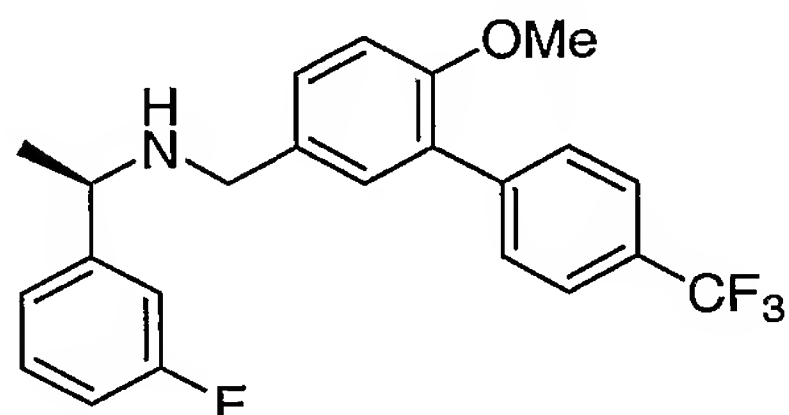


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**Example 73**

(1R)-1-(3-fluorophenyl)-N-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

5



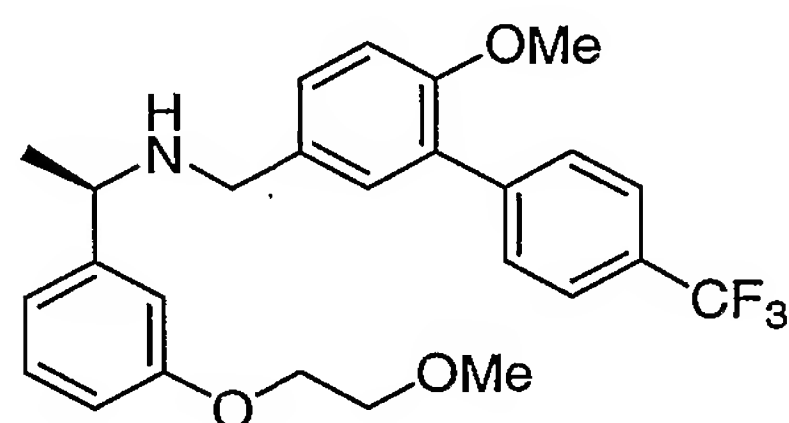
MS(EI) calcd for  $C_{23}H_{22}F_4NO$  ( $MH^+$ ) 404.1, Found 404.1, 265.1.

10

**Example 74**

(1R)-1-(3-((2-(methyloxy)ethyl)oxy)phenyl)-N-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

15



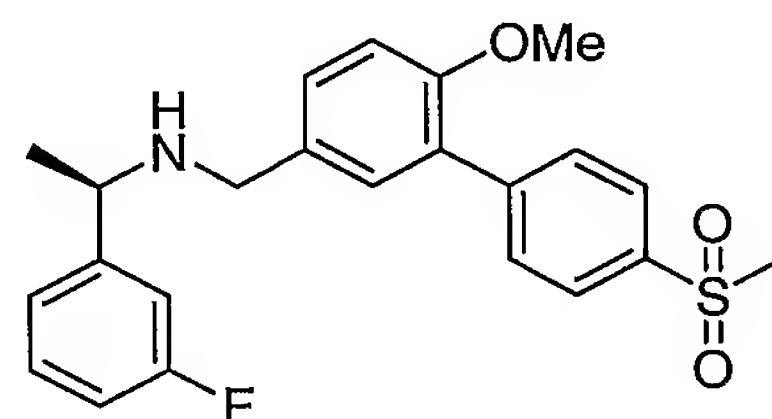
MS(EI) calcd for  $C_{26}H_{29}F_3NO_3$  ( $MH^+$ ) 460.2, Found 460.2, 265.1.

20

**Example 75**

(1R)-1-(3-fluorophenyl)-N-(((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

25



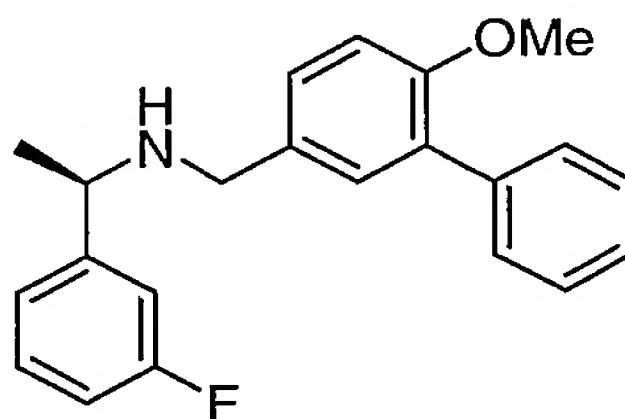
MS(EI) calcd for  $C_{23}H_{25}FNO_3S$  ( $MH^+$ ) 414.1, Found 414.2, 275.2.

30

**Example 76**

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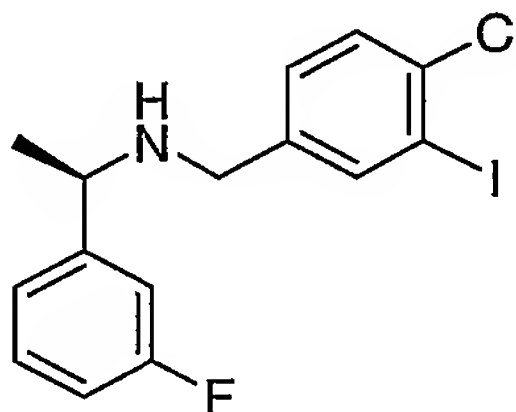
(1R)-1-(3-fluorophenyl)-N-((6-(methoxy)-1,1'-biphenyl-3-yl)methyl)ethanamine



5 MS(EI) calcd for  $C_{22}H_{23}FNO$  ( $MH^+$ ) 336.2, Found 336.2, 197.1.

**Example 77**

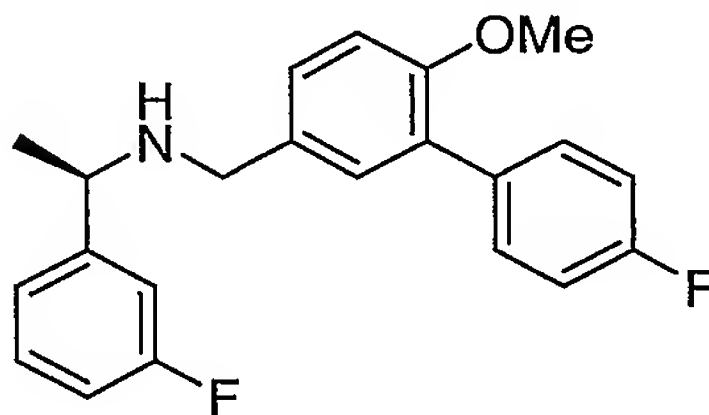
10 (1R)-N-((4-chloro-3-iodophenyl)methyl)-1-(3-fluorophenyl)ethanamine



15 MS(EI) calcd for  $C_{15}H_{15}ClIN$  ( $MH^+$ ) 390.0, Found 390.0, 251.0, 123.1.

**Example 78**

20 (1R)-N-((4'-fluoro-6-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-fluorophenyl)ethanamine

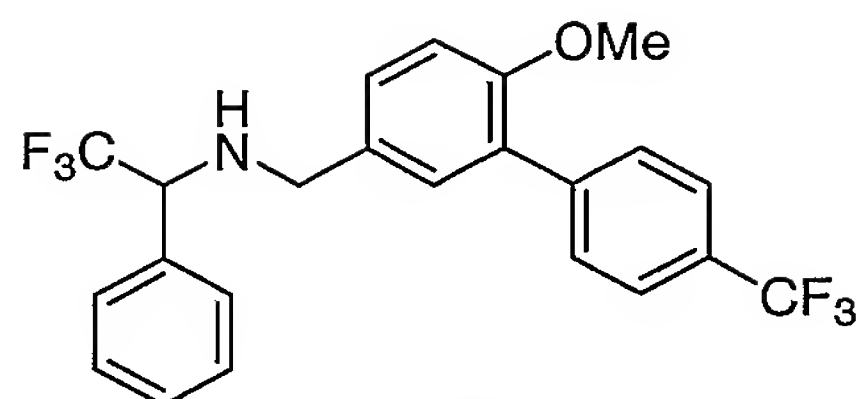


25 MS(EI) calcd for  $C_{22}H_{22}F_2NO$  ( $MH^+$ ) 354.1, Found 354.1, 215.1.

**Example 79**

30 2,2,2-trifluoro-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

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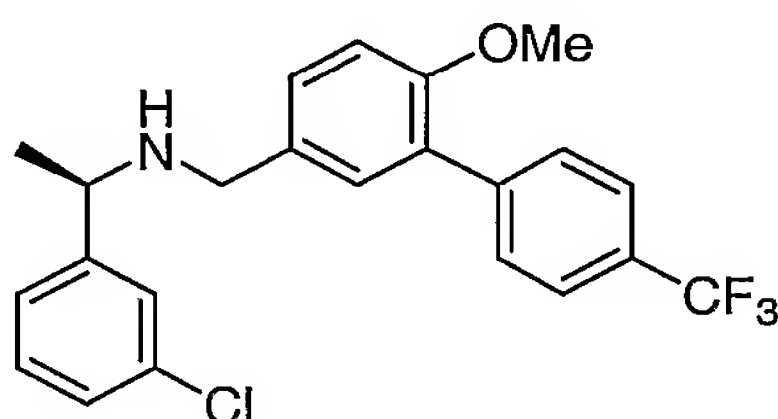


MS(EI) calcd for  $C_{23}H_{20}F_6NO$  ( $MH^+$ ) 440.0, Found 439.9, 264.7.

5

**Example 80**

(1R)-1-(3-chlorophenyl)-N-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



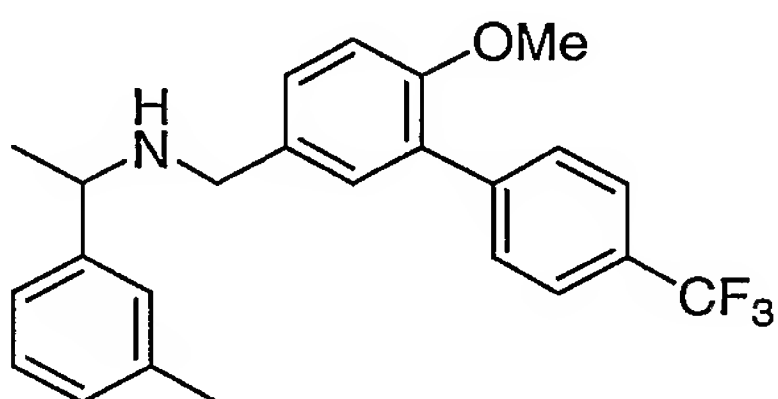
10

MS(EI) calcd for  $C_{23}H_{21}ClF_3NO$  420.87 ( $MH^+$ ), Found: 420.1; 422.1 265.1

15

**Example 81**

N-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-methylphenyl)ethanamine



20

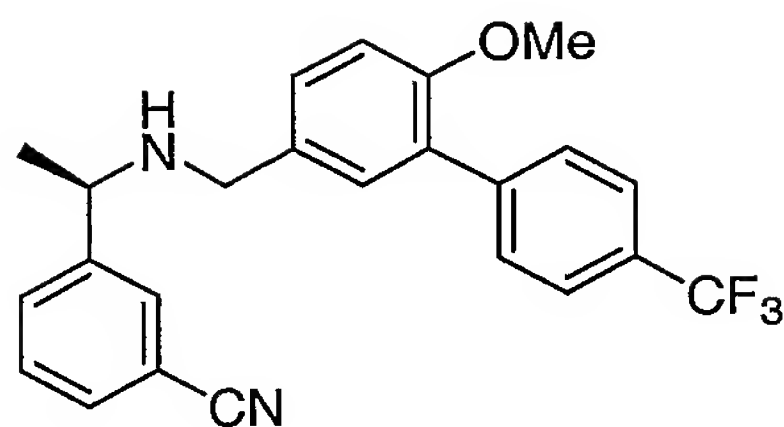
MS(EI) calcd for  $C_{24}H_{24}F_3NO$  400.45 ( $MH^+$ ), Found: 400.1; 265.1

25

**Example 82**

3-(1-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)amino)ethyl)benzonitrile

- 120 -



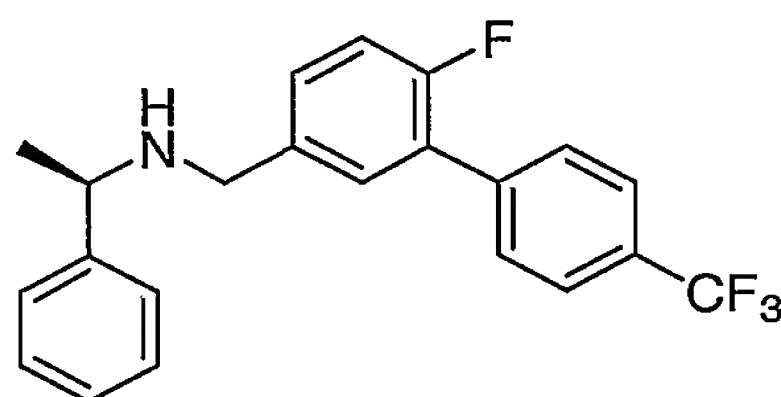
MS(EI) calcd for  $C_{24}H_{21}F_3N_2O$  411.44 (MH+) Found: 411.3; 265.1

5

**Example 83**

(1R)-N-((6-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

10



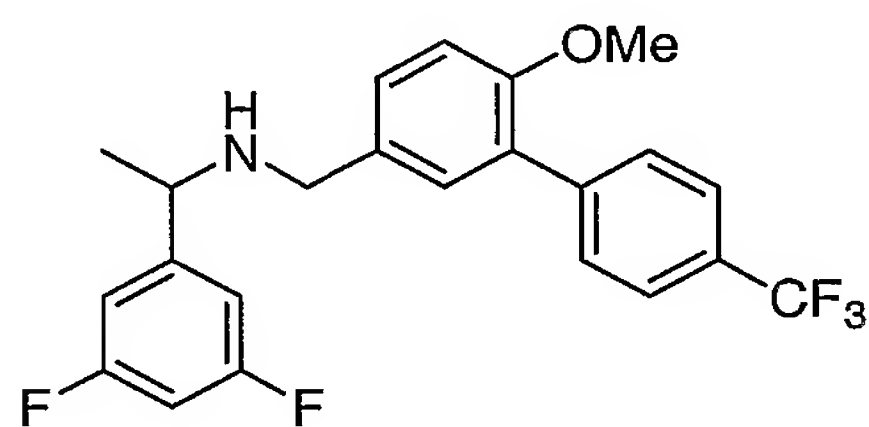
MS(EI) calcd for  $C_{22}H_{19}F_4N$  374.30 (MH+) Found: 374.2;

15

**Example 84**

1-(3,5-difluorophenyl)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

20



MS(EI) calcd for  $C_{23}H_{20}F_5NO$  422.41 (MH+) Found: 422.2; 265.2

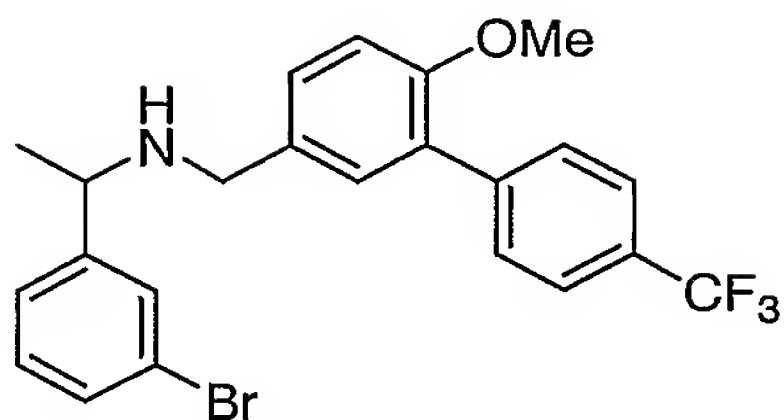
25

**Example 85**

1-(3-bromophenyl)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

30

- 121 -



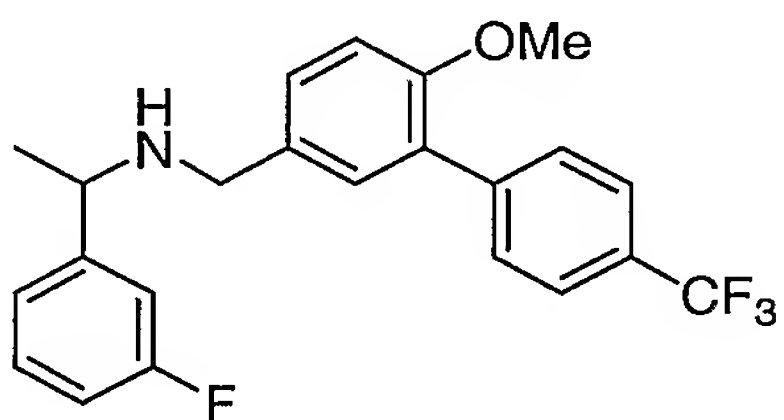
MS(EI) calcd for  $C_{23}H_{21}BrF_3NO$  465.32 (MH<sup>+</sup>) Found: 466.0; 265.1

5

**Example 86**

1-(3-fluorophenyl)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

10



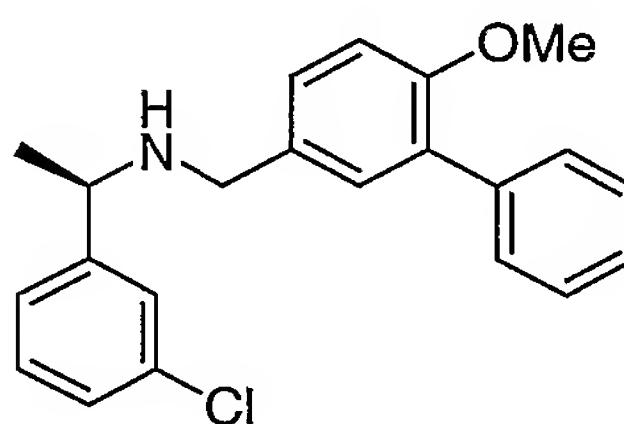
MS(EI) calcd for  $C_{23}H_{21}F_4NO$  404.42 (MH<sup>+</sup>) Found: 404.2; 265.1

15

**Example 87**

(1R)-1-(3-chlorophenyl)-N-((6-(methoxy)-1,1'-biphenyl-3-yl)methyl)ethanamine

20



MS(EI) calcd for  $C_{22}H_{22}ClNO$  352.88 (MH<sup>+</sup>) Found: 353.1; 197.1

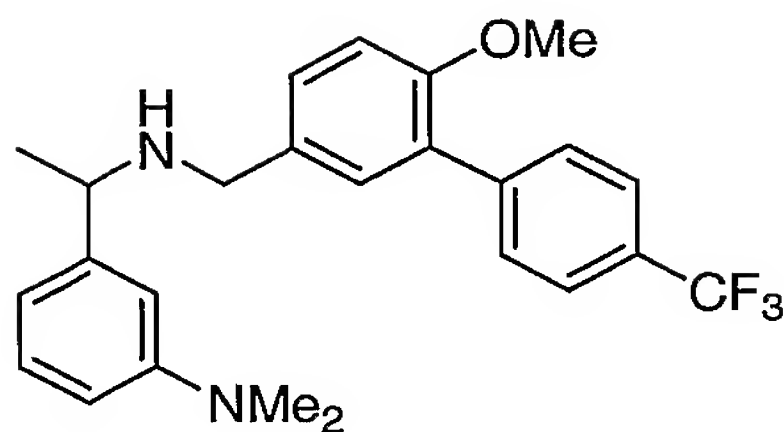
25

**Example 88**

N-1-(3-(dimethylamino)phenyl)ethyl)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)amine

30

- 122 -



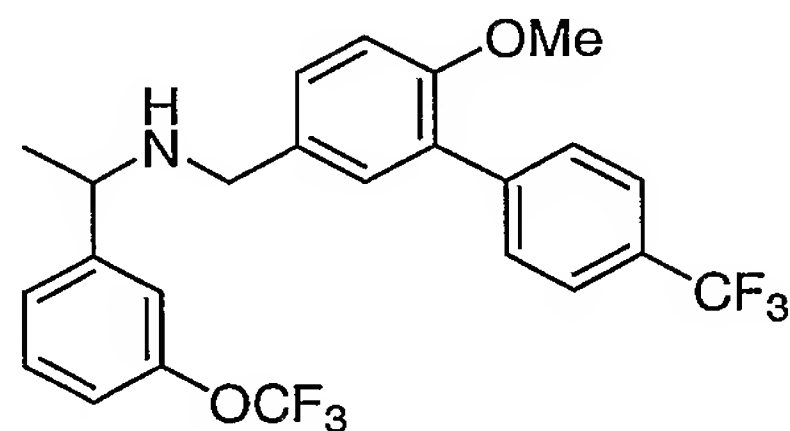
MS(EI) calcd for  $C_{25}H_{27}F_3 N_2O$  429.50 (MH+) Found: 429.2; 265.1

5

**Example 89**

N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-((trifluoromethyl)oxy)phenyl)ethanamine

10



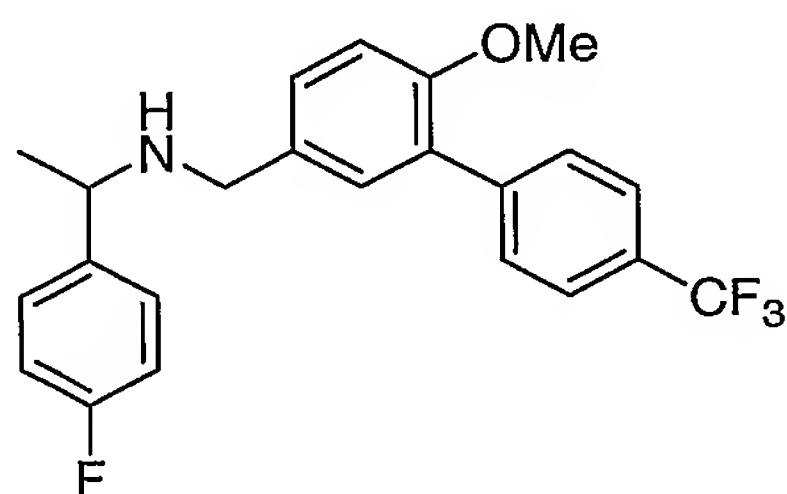
MS(EI) calcd for  $C_{24}H_{21}F_6NO_2$  470.42 (MH+) Found: 470.1; 265.1

15

**Example 90**

1-(4-fluorophenyl)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

20



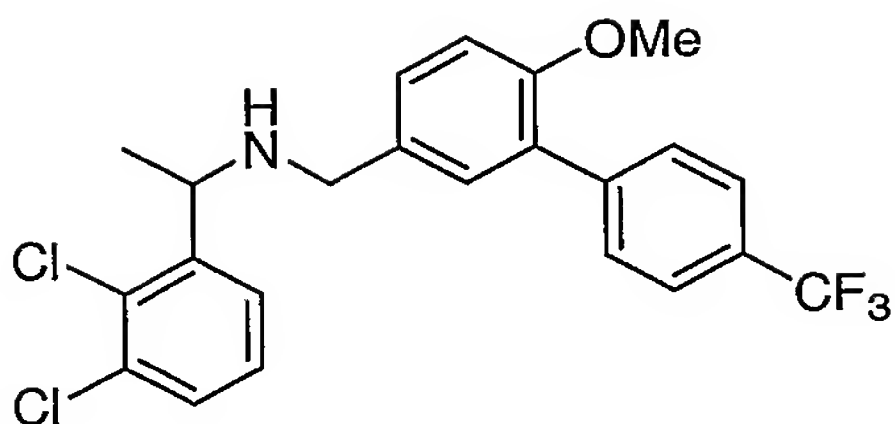
MS(EI) calcd for  $C_{23}H_{21}F_4NO$  404.42 (MH+) Found: 404.2; 265.1

25

**Example 91**

1-(2,3-dichlorophenyl)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

- 123 -



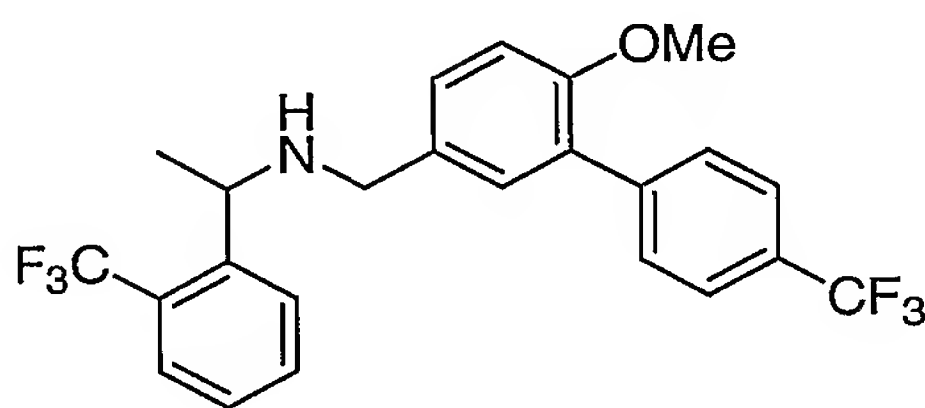
MS(EI) calcd for  $C_{23}H_{20}Cl_2F_3NO$  455.32 (MH<sup>+</sup>) Found: 454.0; 456.0

5

**Example 92**

N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(2-(trifluoromethyl)phenyl)ethanamine

10



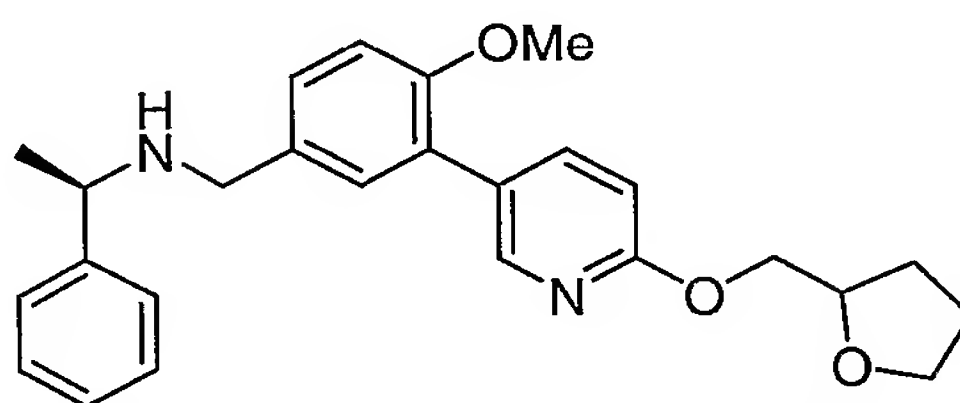
MS(EI) calcd for  $C_{24}H_{21}F_6NO$  454.42 (MH<sup>+</sup>) Found: 454.2; 265.1

15

**Example 93**

(1R)-N-((4-(methoxy)-3-(6-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

20



MS (ESI, pos. ion) *m/z*: Calc'd for  $C_{26}H_{30}N_2O_3$ : 418.5 g/mol. Found: (M+1) 418.7, 334.9, 297.7

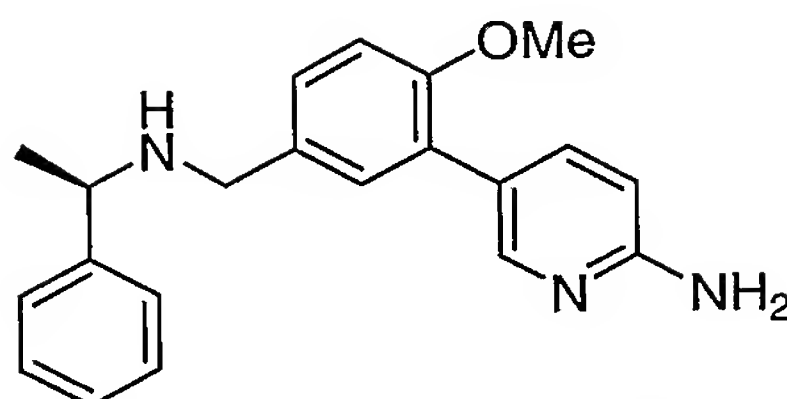
25

**Example 94**

5-(2-(methoxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine



- 124 -



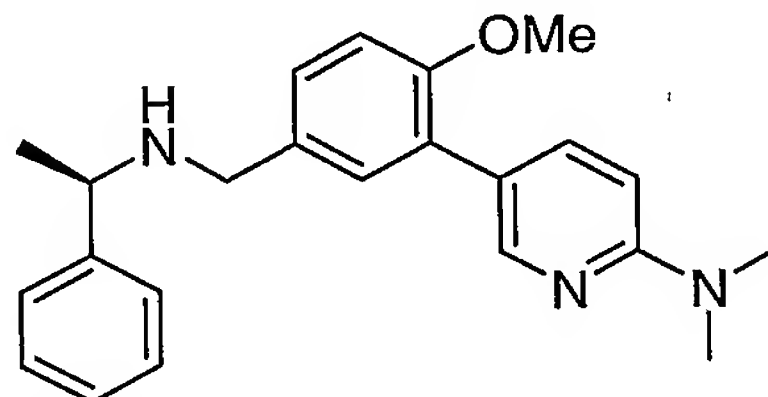
MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O: 333.43 g/mol. Found: (M+1) 334.1, 213.2

5

**Example 95**

N,N-dimethyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine

10



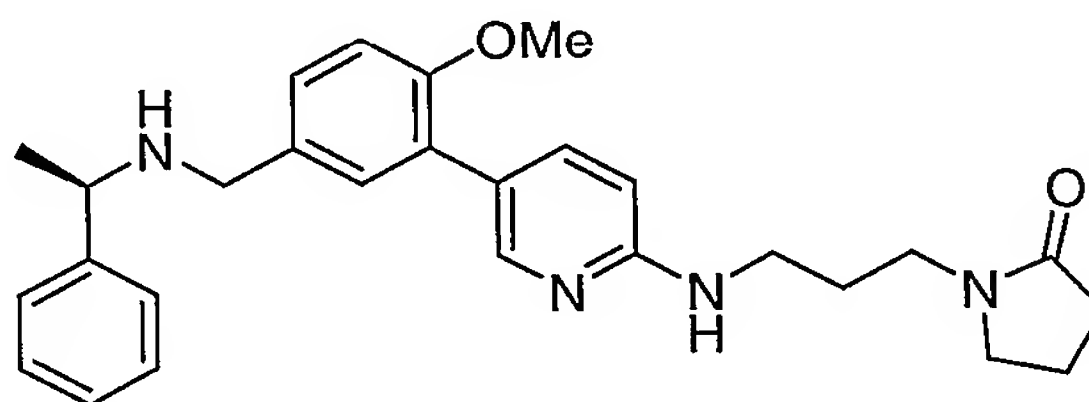
MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O: 361.48 g/mol. Found: (M+1) 362.0, 241.2

15

**Example 96**

1-(3-((5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)amino)propyl)-2-pyrrolidinone

20



MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>28</sub>H<sub>34</sub>N<sub>4</sub>O<sub>2</sub>: 458.60 g/mol. Found: (M+1) 458.8, 355.0, 337.7, 306.0, 239.1

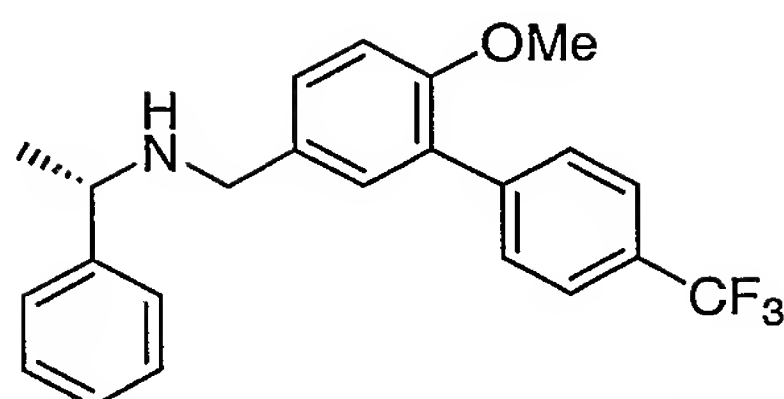
25

**Example 97**

(1S)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

30

- 125 -



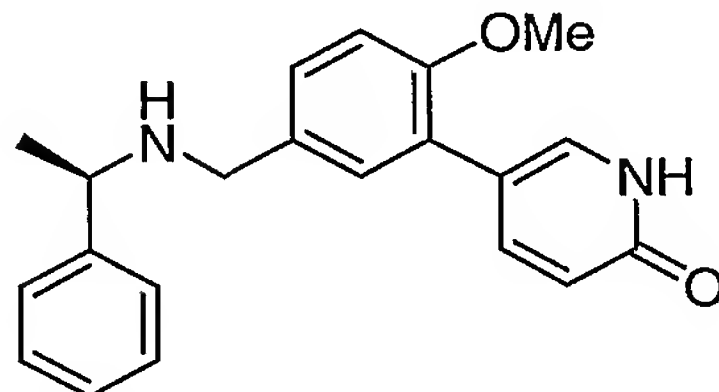
MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>23</sub>H<sub>22</sub>F<sub>3</sub>NO: 385.43 g/mol. Found: (M+1) 385.9, 264.6, 245.2

5

**Example 98**

5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2(1H)-pyridinone

10



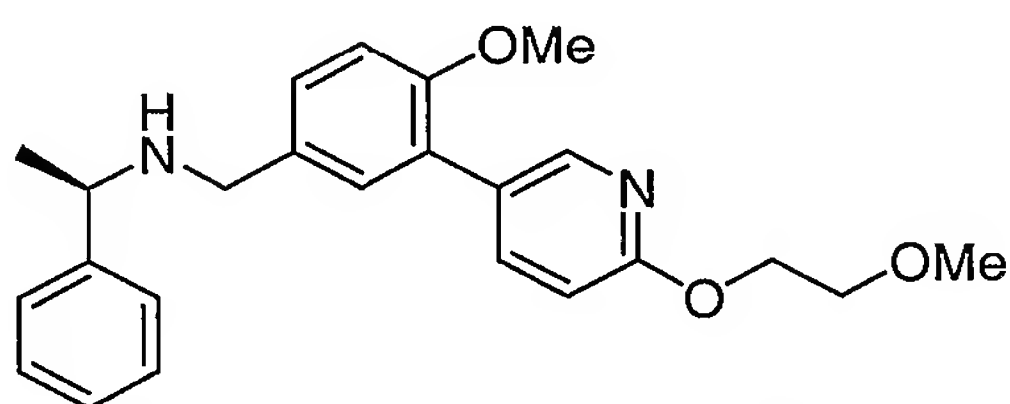
MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: 334.42 g/mol. Found: (M+1) 334.9, 214.2

15

**Example 99**

(1R)-N-((4-(methyloxy)-3-(6-((2-(methyloxy)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

20



MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>: 392.50 g/mol. Found: (M+1) 392.9, 334.9, 271.9, 226.2

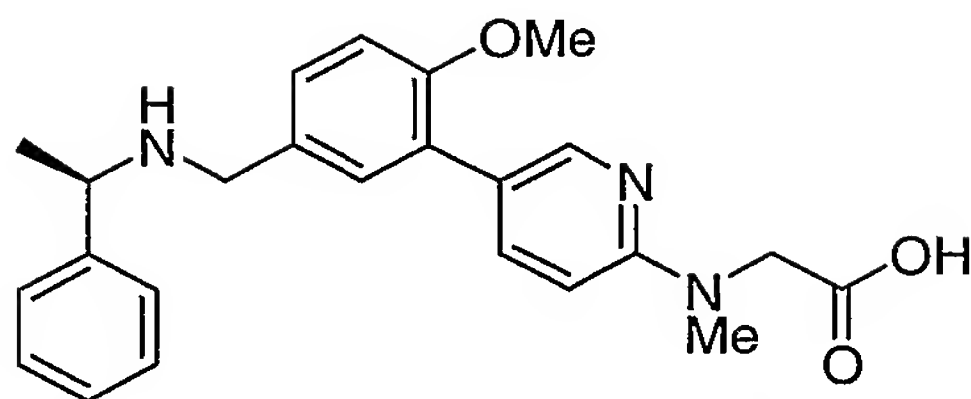
25

**Example 100**

N-methyl-N-(5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinylglycine

30

- 126 -



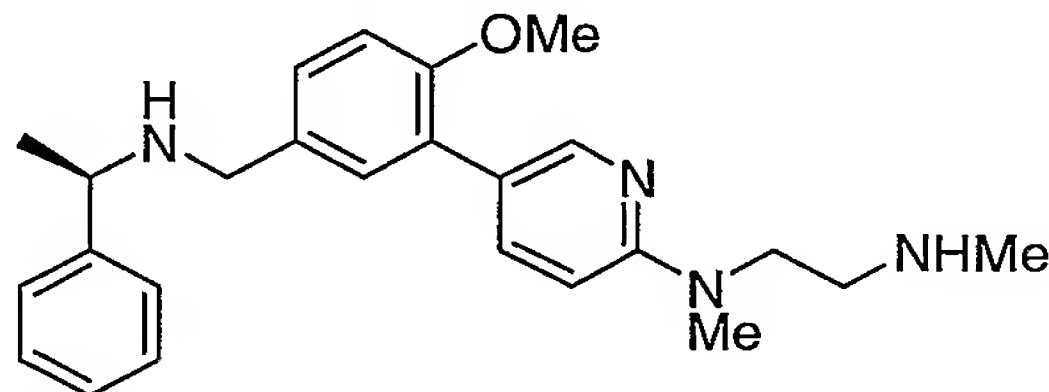
MS (ESI, pos. ion)  $m/z$ : Calc'd for  $C_{24}H_{27}N_3O_3$ : 405.50 g/mol. Found: (M+1) 406.3, 284.9

5

**Example 101**

N-1-,N-2-dimethyl-N-1-(5-(2-(methyloxy)-5-(((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)-1,2-ethanediamine

10



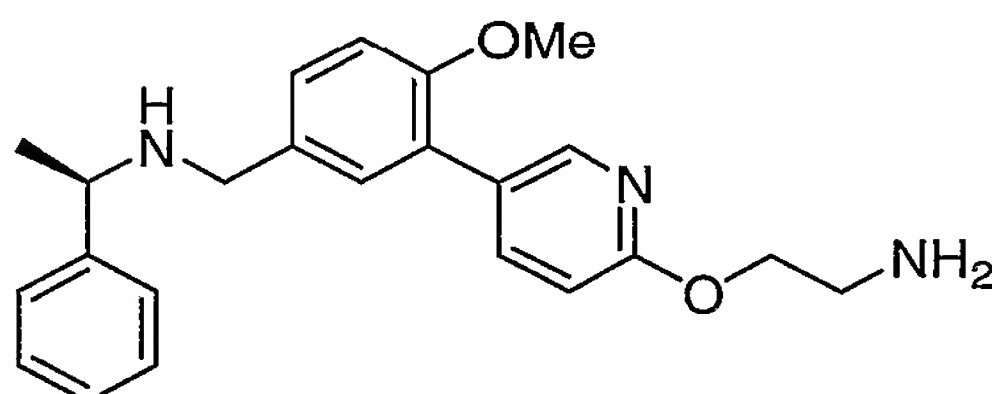
MS (ESI, pos. ion)  $m/z$ : Calc'd for  $C_{25}H_{32}N_4O$ : 404.56 g/mol. Found: (M+1) 404.8, 373.7, 301.0, 284.0, 270.0

15

**Example 102**

(1R)-N-((3-(6-((2-aminoethyl)oxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethyl)amine

20



MS (ESI, pos. ion)  $m/z$ : Calc'd for  $C_{23}H_{27}N_3O_2$ : 377.49 g/mol. Found: (M+1) 377.8, 274.1, 256.9

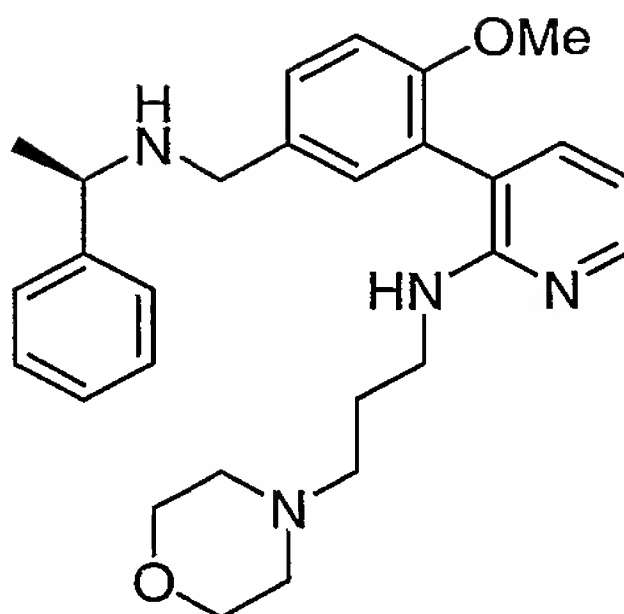
25

**Example 103**

3-(2-(methyloxy)-5-(((1R)-1-phenylethyl)amino)methyl)phenyl)-N-(3-(4-morpholinyl)propyl)-2-pyridinamine

30

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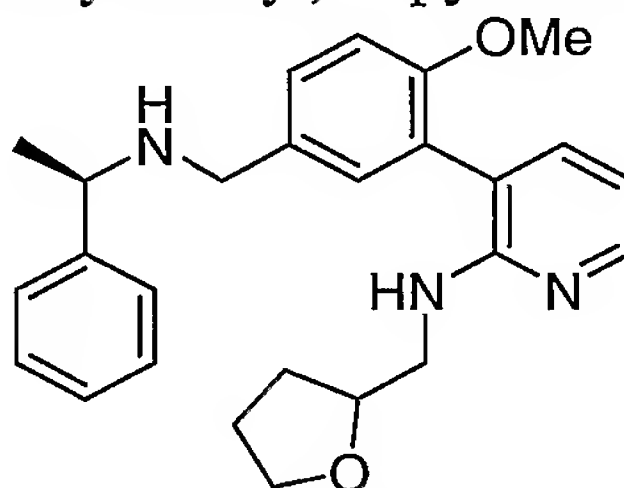


MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>28</sub>H<sub>36</sub>N<sub>4</sub>O<sub>2</sub>: 460.62 g/mol. Found: (M+1) 461.1, 356.8

5

**Example 104**

3-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-N-(tetrahydro-2-furanylmethyl)-2-pyridinamine



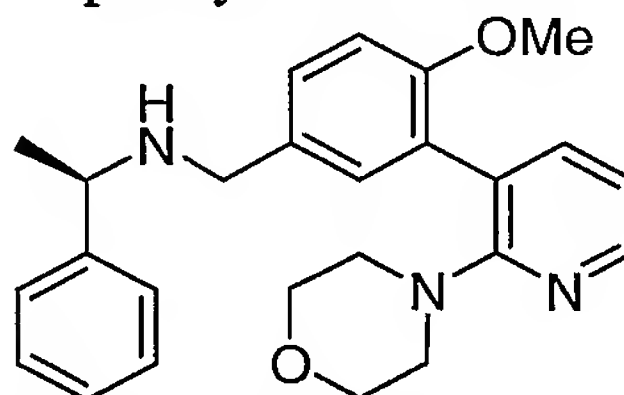
10

MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>: 417.55 g/mol. Found: (M+1) 418.1, 297.1, 265.1

15

**Example 105**

(1R)-N-((4-(methyloxy)-3-(2-(4-morpholinyl)-3-pyridinyl)phenyl)methyl)-1-phenylethylamine



20

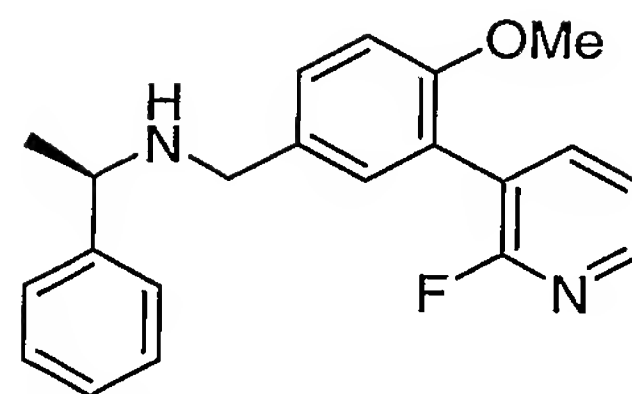
MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>: 403.52 g/mol. Found: (M+1) 404.2, 283.0

25

**Example 106**

(1R)-N-((3-(2-fluoro-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethylamine

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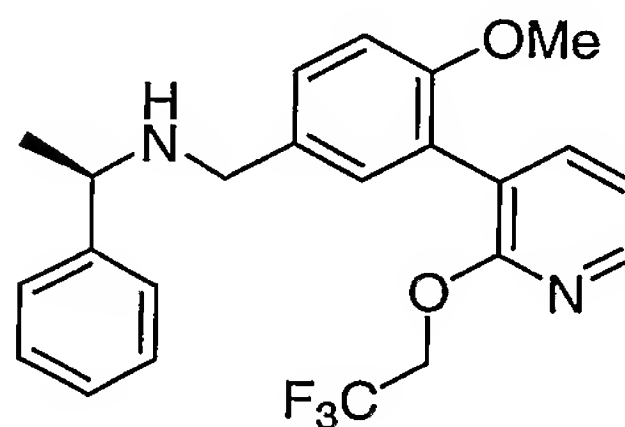
MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>21</sub>H<sub>21</sub>FN<sub>2</sub>O: 336.41 g/mol. Found: (M+1) 336.9, 233.1, 217.1

5

**Example 107**

(1R)-N-((4-(methoxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

10



MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>23</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: 416.44 g/mol. Found: (M+1) 416.7, 295.8

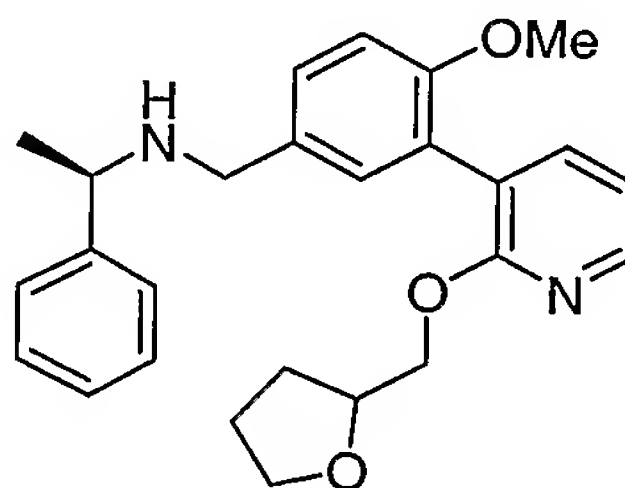
15

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**Example 108**

(1R)-N-((4-(methoxy)-3-(2-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

20



MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>: 418.54 g/mol. Found: (M+1) 419.2, 298.1, 216.1

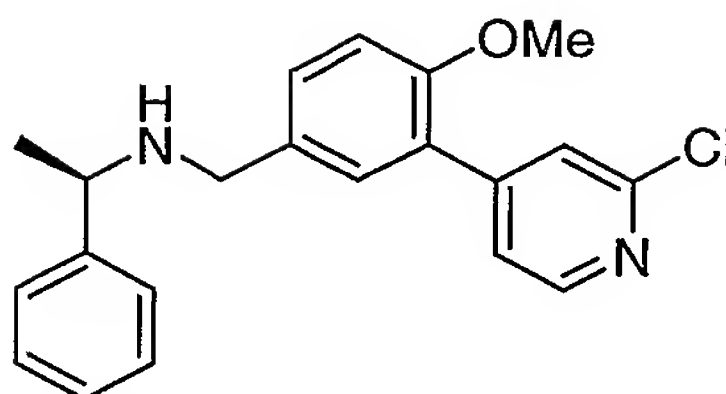
25

**Example 109**

(1R)-N-(3-(2-chloropyrid-4-yl)-4-methoxyphenyl)methyl-N-1-phenylethylamine

30

- 129 -



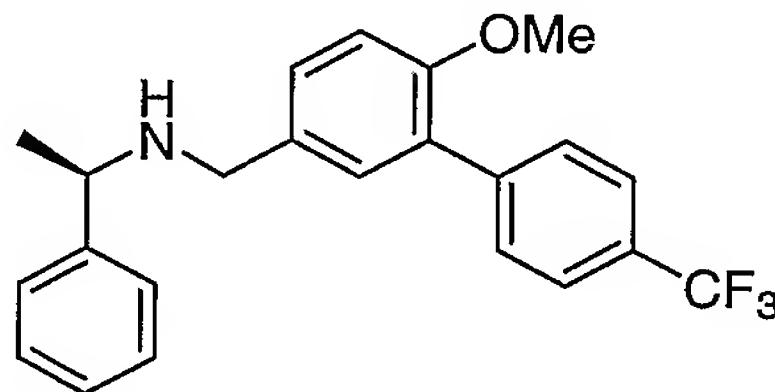
MS (ESI, pos. ion) *m/z*: Calc'd for C<sub>21</sub>H<sub>21</sub>ClN<sub>2</sub>O: 352.86 g/mol. Found: (M+1) 353.0 (d), 231.9 (d)

5

**Example 110**

(1R)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine Prepared using Method C.

10



MW 385.427  
Mass found: 265, 386

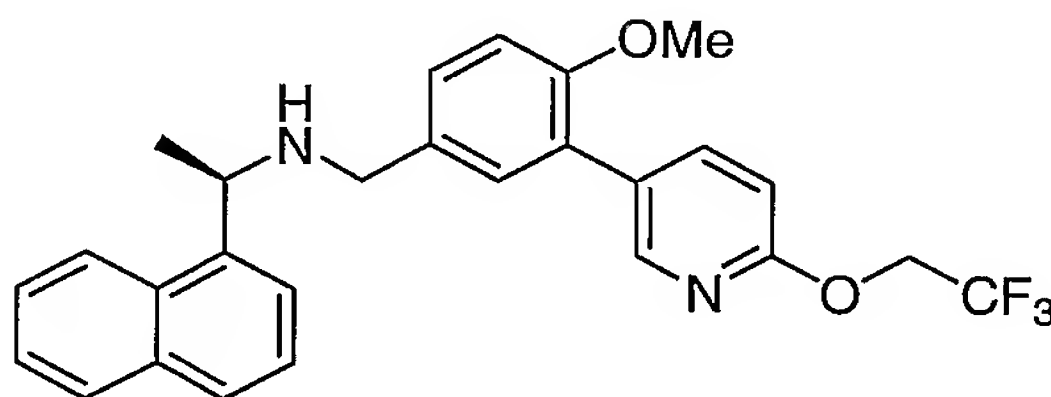
15

\*

**Example 111**

(1R)-N-((4-(methoxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine Prepared using Method C.

20



MW 466.5  
Mass found: 467, 155

25

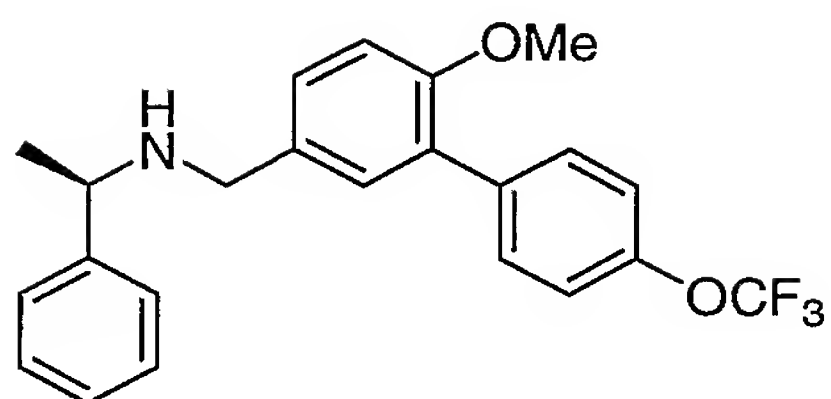
**Example 112**

(1R)-N-((6-(methoxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

30

Prepared using Method C.

- 130 -

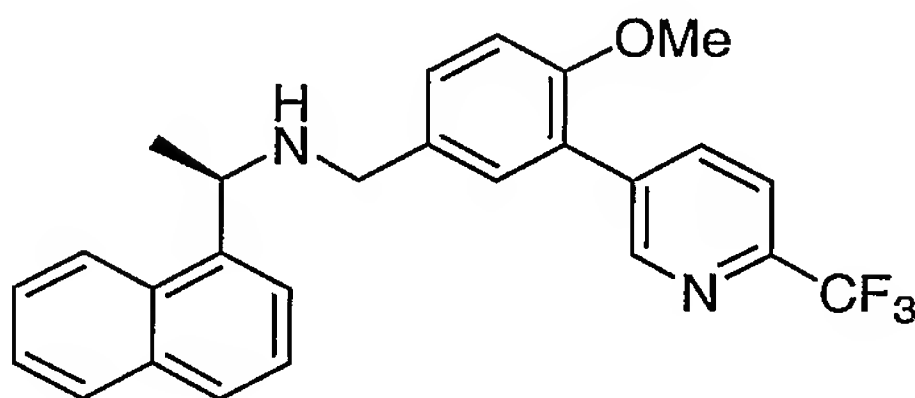


MW 401.426  
Mass found: 402, 803, 917

**Example 113**

(1R)-N-((4-(methoxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

Prepared using Method C.

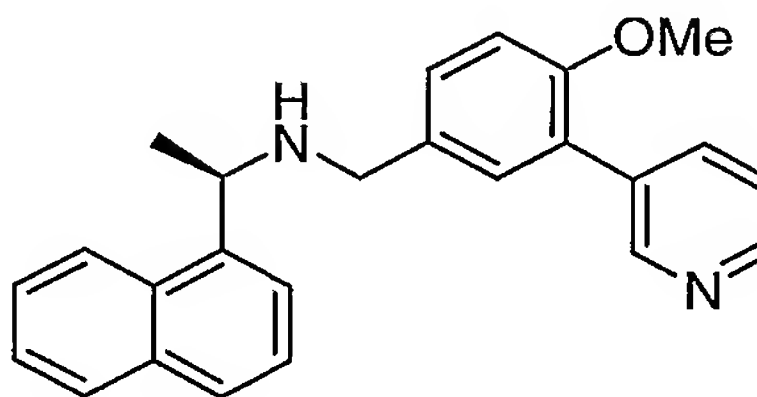


MW 436.475  
Mass found: 437, 478

**Example 114**

(1R)-N-((4-(methoxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

Prepared using Method A.



MW 368.478  
Mass found: 369, 155

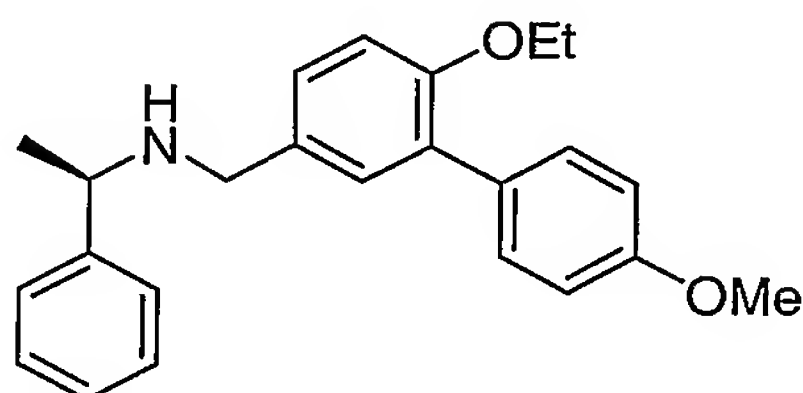
**Example 115**



- 131 -

(1R)-N-((6-(ethoxy)-4'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

5 Prepared using Method C.



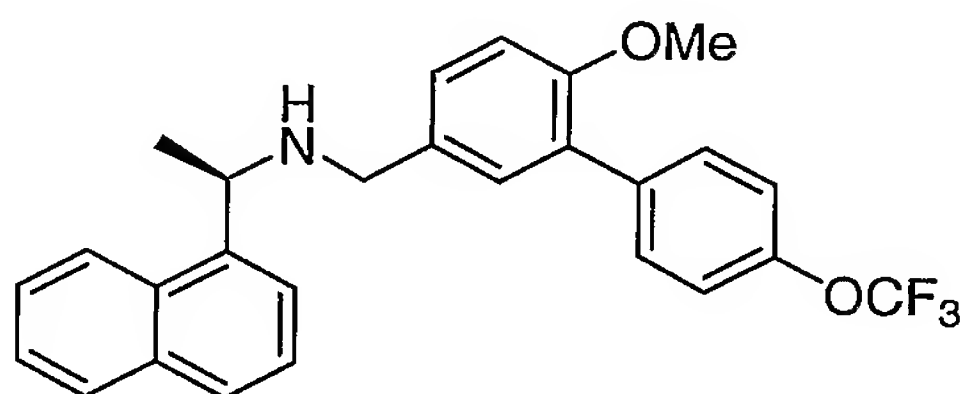
10

MW 361.482  
Mass found: 362

### Example 116

15 (1R)-N-((6-(methoxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

Prepared using Method C.



20

MW 451.486  
Mass found: 452, 155

25

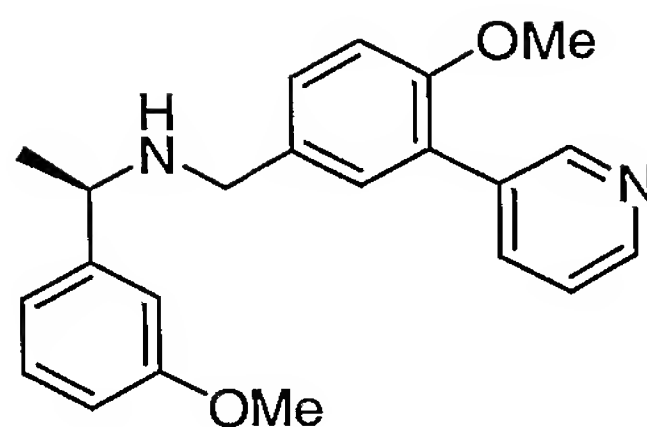
Examples 117-252 were prepared using Method A:

30

### Example 117

(1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine

- 132 -



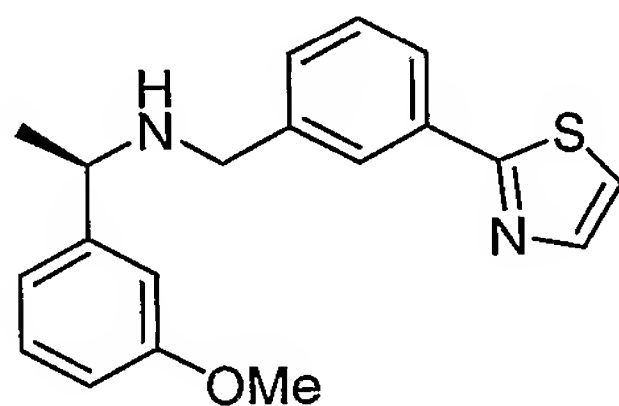
MW 348.444

Mass found: 198, 349

5

**Example 118**

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine



10

MW 324.446

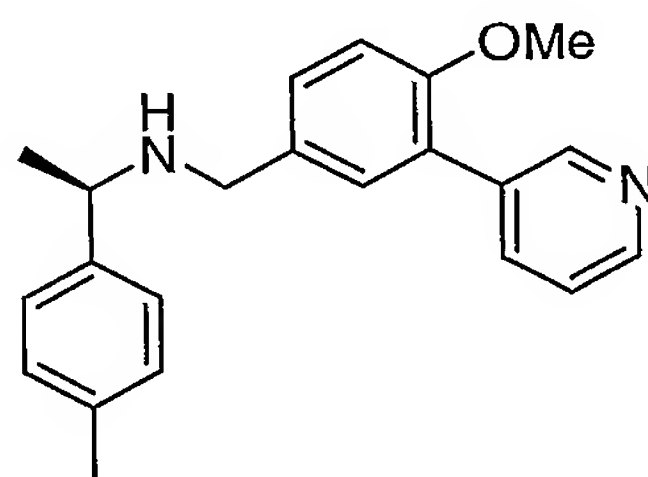
Mass found: 325, 649

15

**Example 119**

(1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine

20



MW 332.445

Mass found: 333, 779

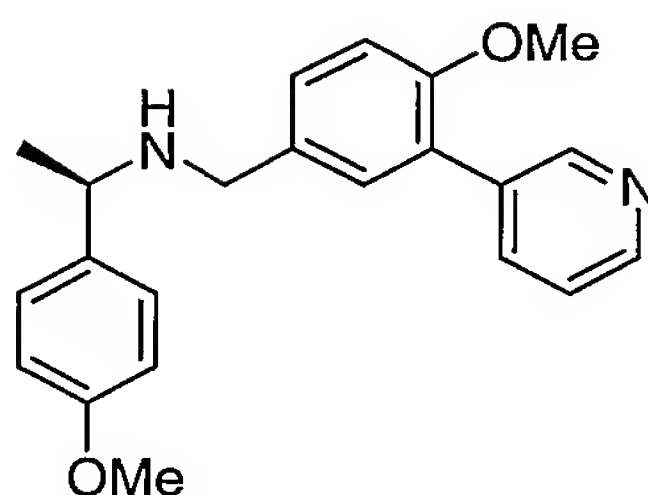
25

**Example 120**

(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine

30

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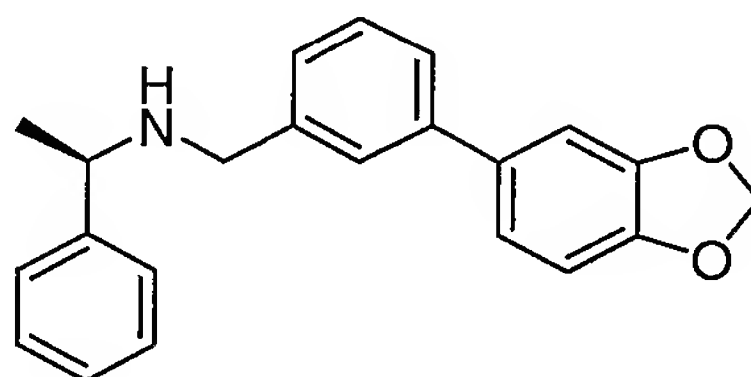


MW 348.444

Mass found: 349

**Example 121**

(1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-phenylethanamine

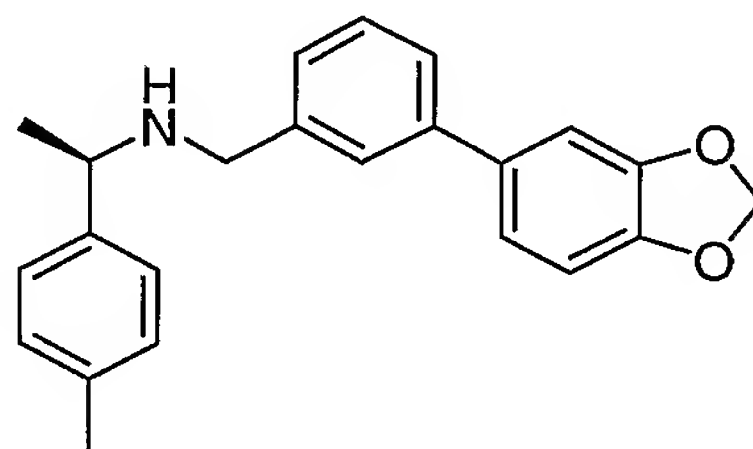


MW 331.413

Mass found: 332, 777

**Example 122**

(1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



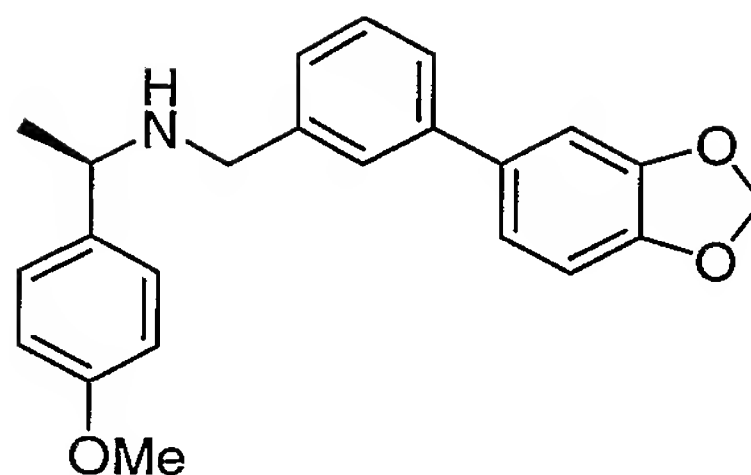
MW 345.44

Mass found: 346

**Example 123**

(1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

- 134 -



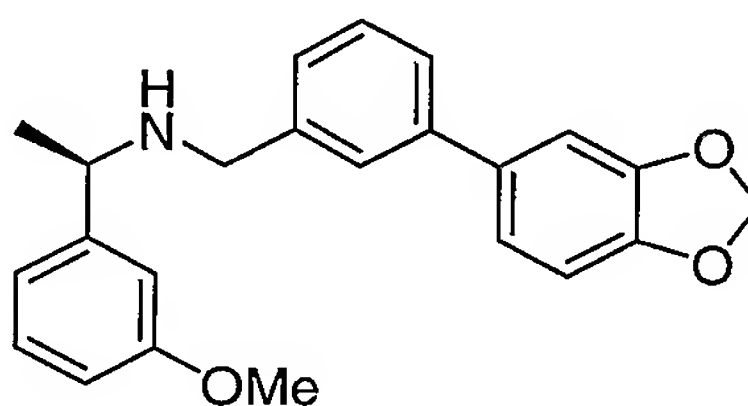
MW 361.439  
Mass found: 362

5

**Example 124**

(1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

10



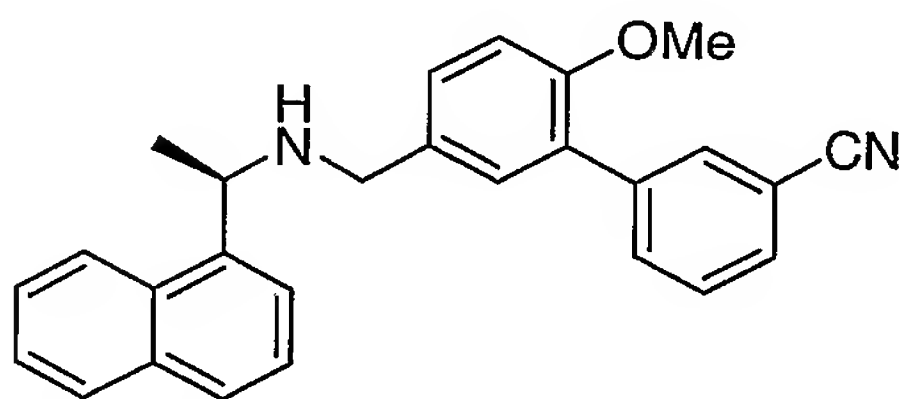
MW 361.439  
Mass found: 362

15

**Example 125**

2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile

20



MW 392.5  
Mass found: 393

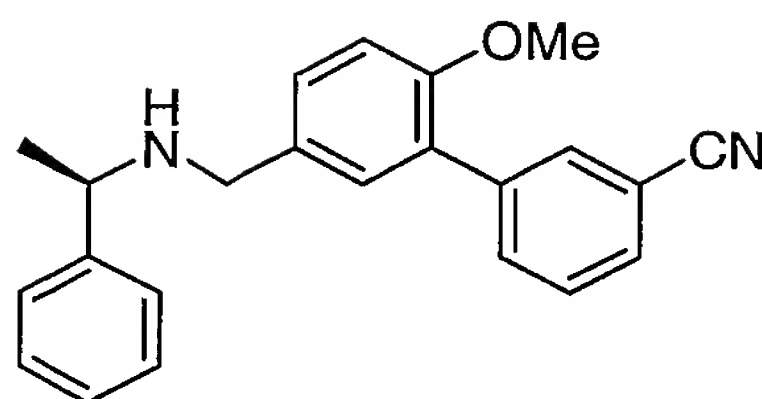
25

**Example 126**

2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile

30

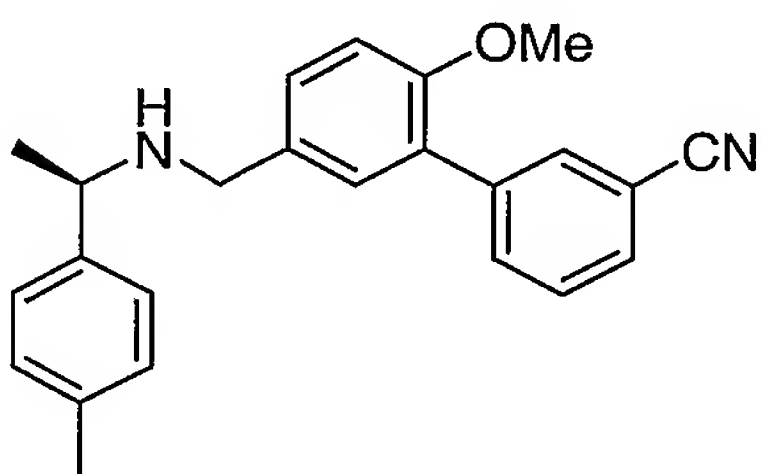
- 135 -



MW 342.44  
Mass found: 343, 384

**Example 127**

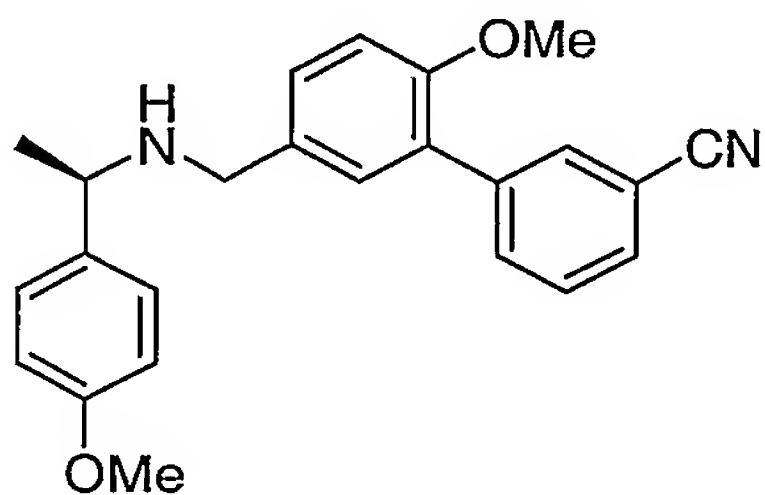
10 2'-(methyloxy)-5'-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile



MW 356.467  
Mass found: 357, 398

**Example 128**

20 2'-(methyloxy)-5'-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile

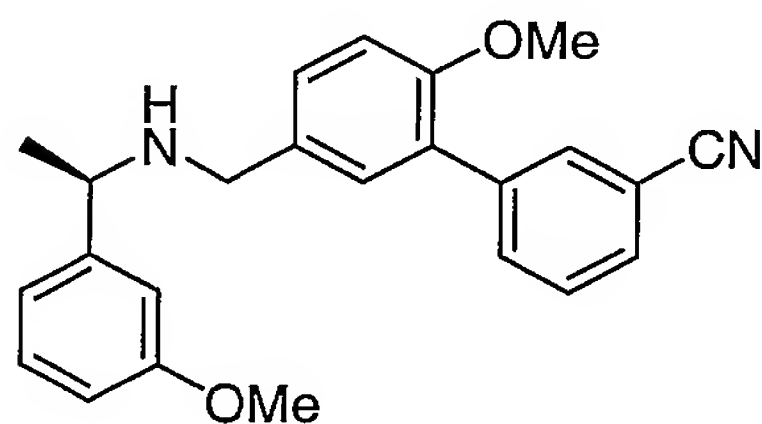


MW 372.466  
Mass found: 373, 414

**Example 129**

- 136 -

2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile



5

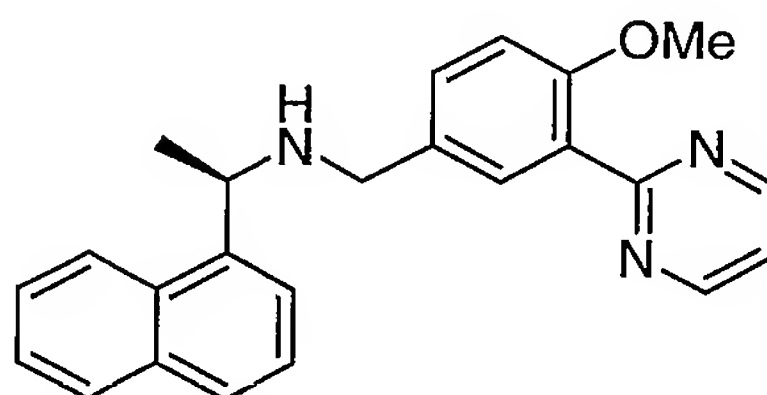
MW 372.466  
Mass found: 373, 414

10

**Example 130**

(1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



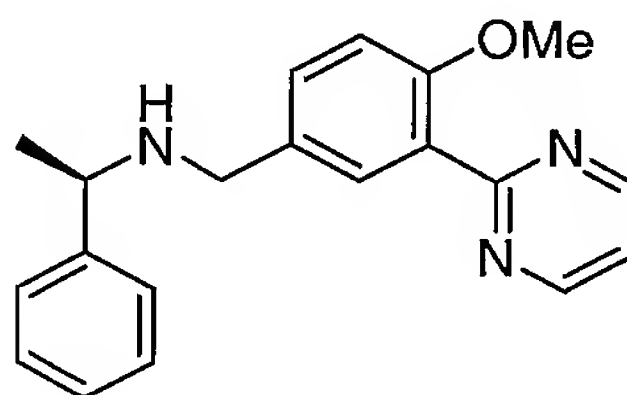
20

MW 369.466  
Mass found: 370, 739

**Example 131**

(1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-phenylethanamine

25



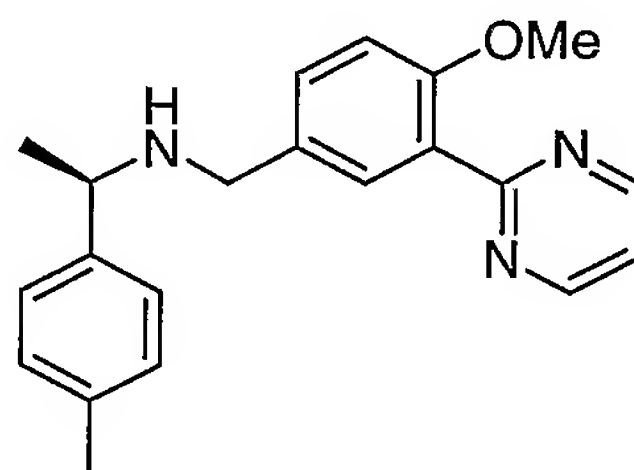
30

MW 319.406  
Mass found: 320

**Example 132**

- 137 -

(1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



5

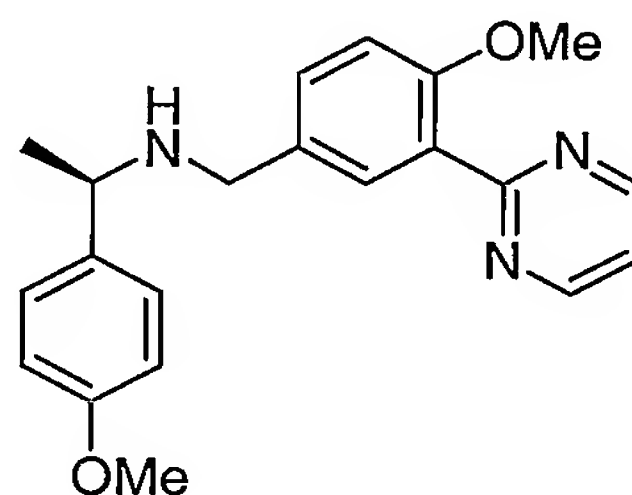
MW 333.433  
Mass found: 334, 667

10

**Example 133**

(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)ethanamine

15



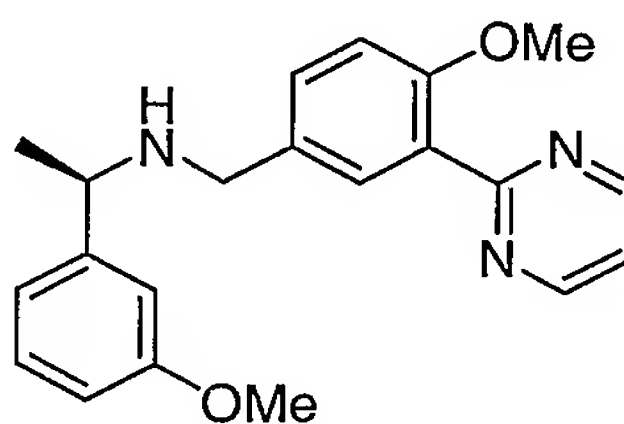
MW 349.432  
Mass found: 350, 699

20

**Example 134**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)ethanamine

25



MW 349.432  
Mass found: 350, 699

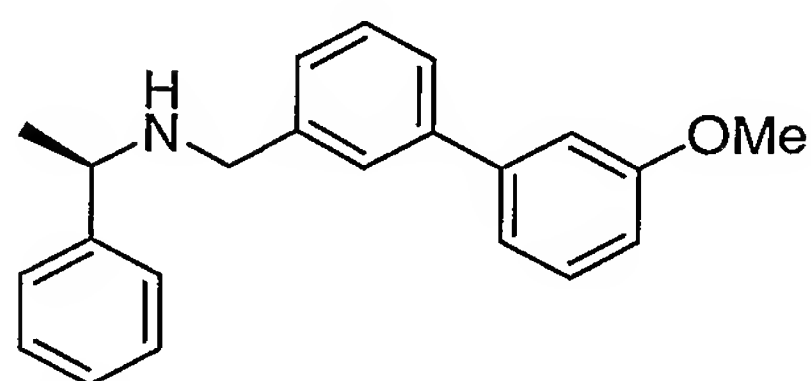
30



- 138 -

**Example 135**

5 (1R)-N-((3'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



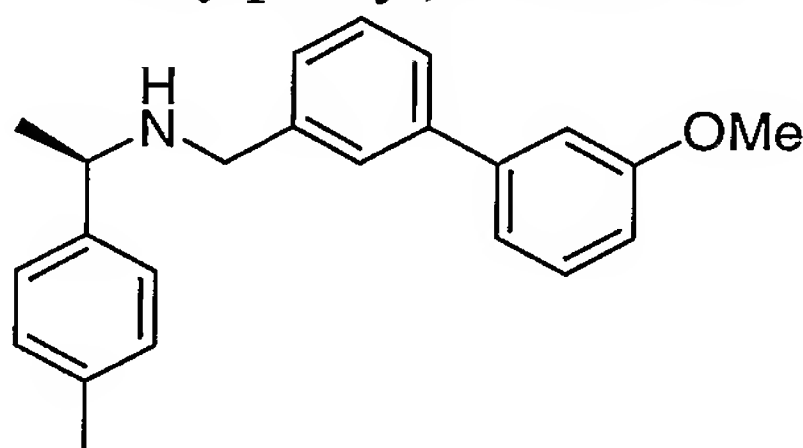
MW 317.43

Mass found: 318, 197, 214

10

**Example 136**

15 (1R)-N-((3'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



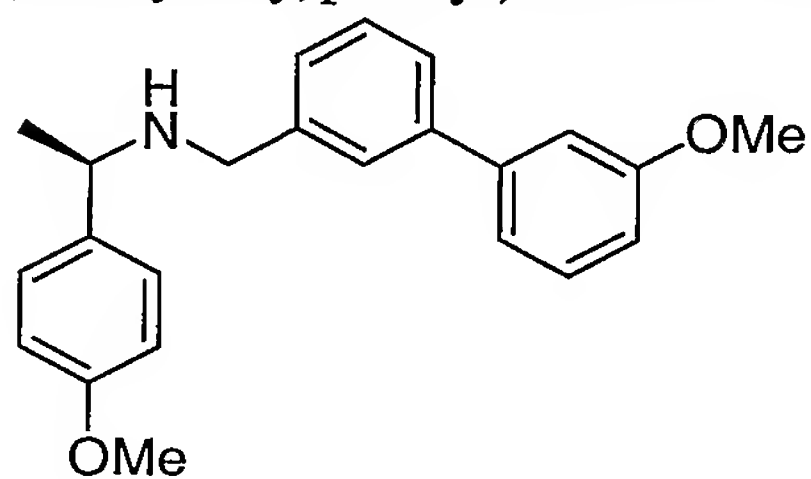
MW 331.457

Mass found: 332, 214

20

**Example 137**

25 (1R)-N-((3'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methoxy)phenyl)ethanamine



MW 347.456

Mass found: 348, 214

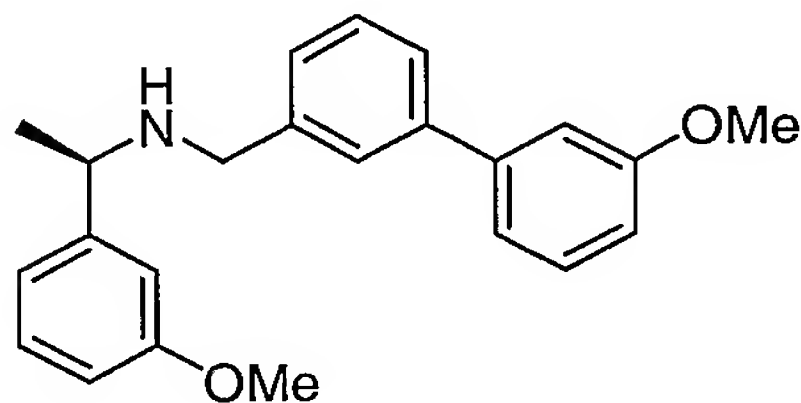
30

- 139 -

**Example 138**

(1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

5



MW 347.456

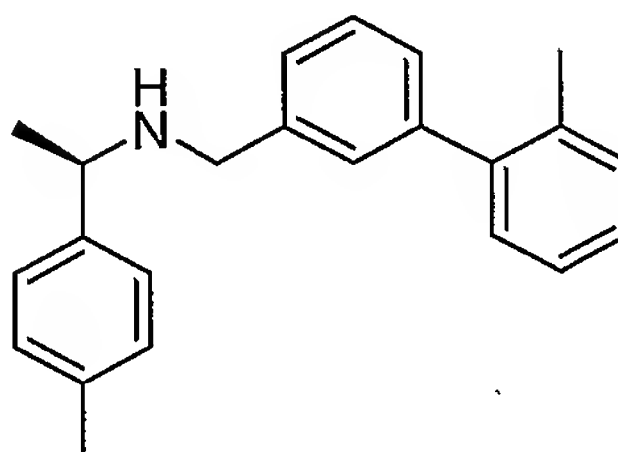
Mass found: 348, 214, 255

10

**Example 139**

(1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine

15



MW 315.457

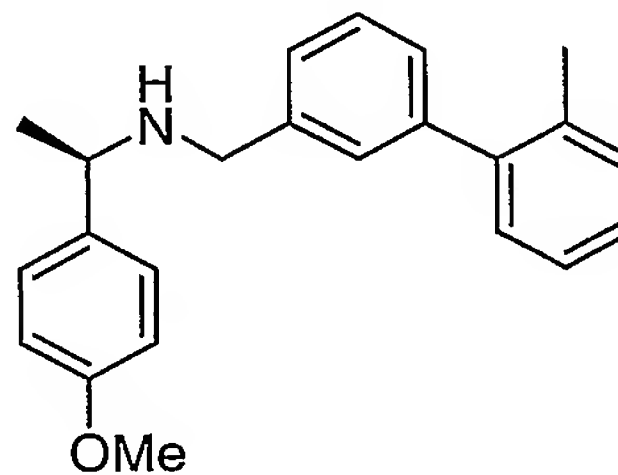
Mass found: 181, 316, 198

20

**Example 140**

(1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

25



MW 331.457

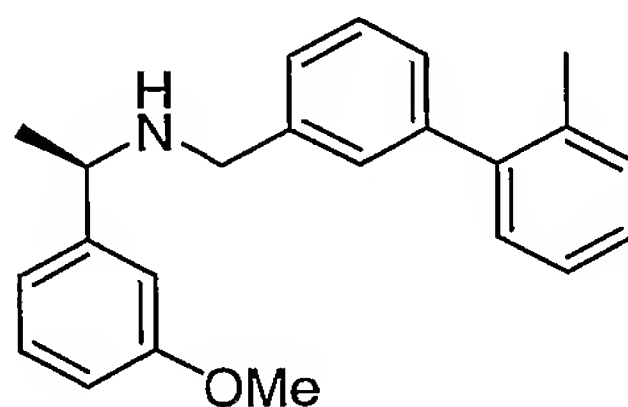
Mass found: 332, 181, 198

30

- 140 -

**Example 141**

(1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

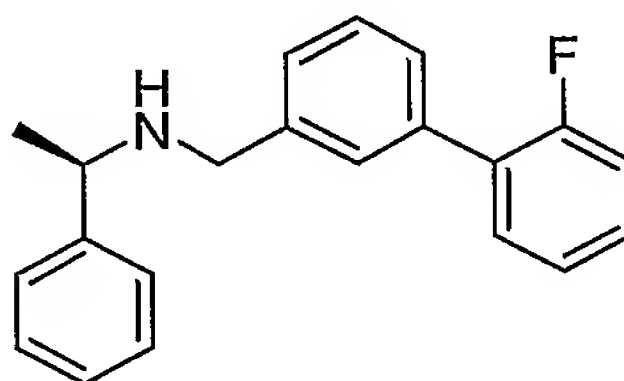


MW 331.457

Mass found: 332, 198, 181

**Example 142**

(1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

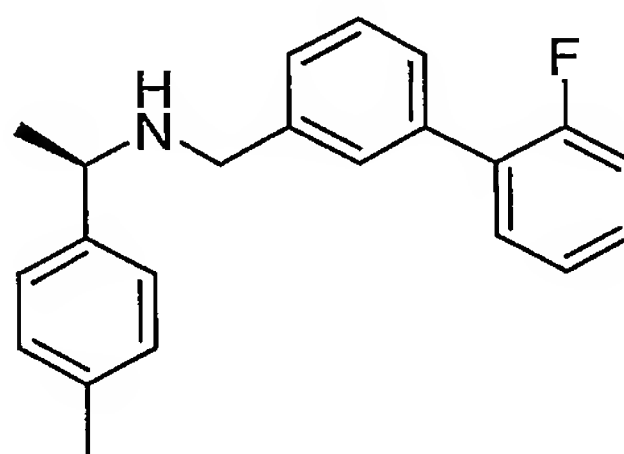


MW 305.394

Mass found: 202, 306, 243

**Example 143**

(1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



MW 319.421

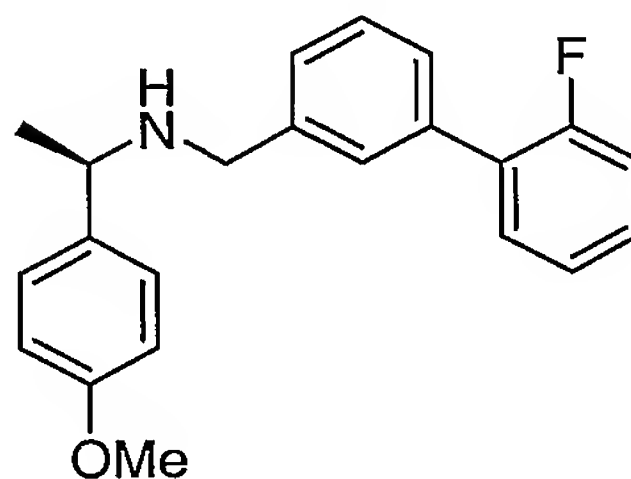
Mass found: 202, 320, 243

- 141 -

**Example 144**

(1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

5



MW 335.42

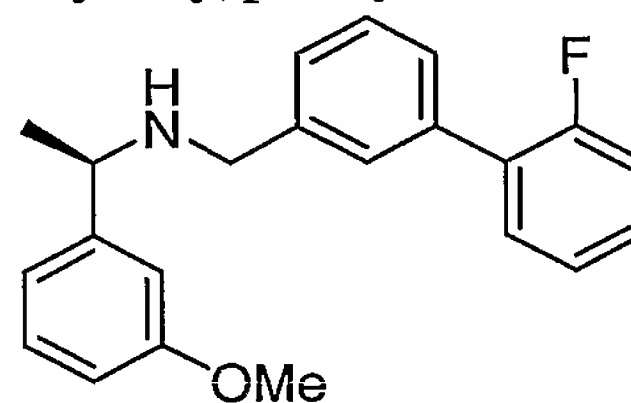
Mass found: 336, 202, 243

10

**Example 145**

(1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

15



MW 335.42

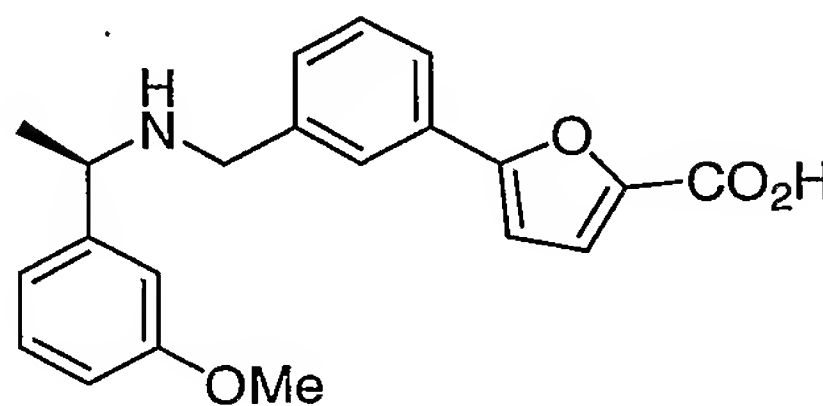
Mass found: 202, 336, 243

20

**Example 146**

5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-furancarboxylic acid

25



MW 381.426

Mass found: 382, 423

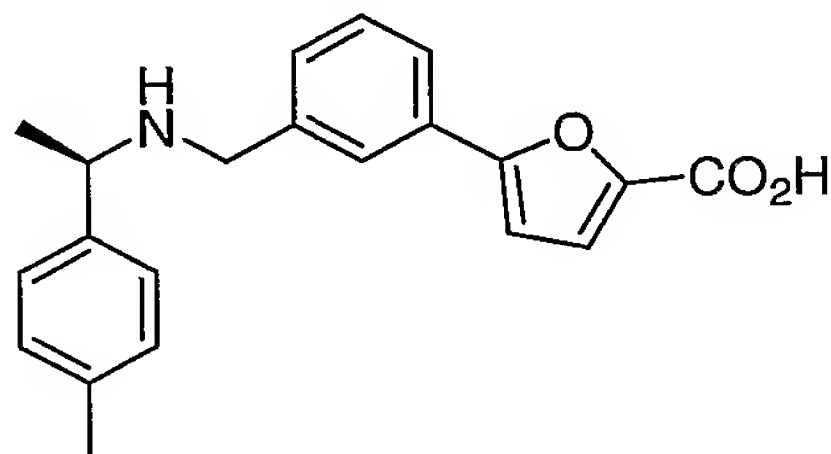
30

- 142 -

**Example 147**

5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-furancarboxylic acid

5



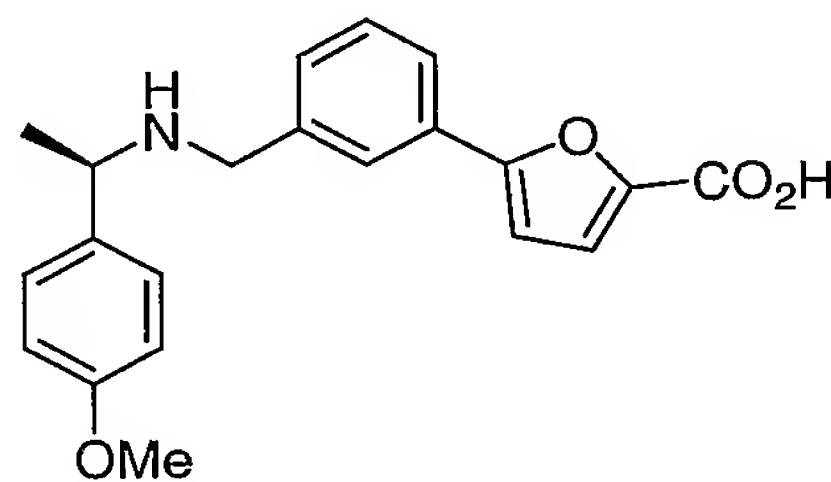
MW 365.427  
Mass found: 366, 731

10

**Example 148**

5-(2-(methyloxy)-5-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-furancarboxylic acid

15



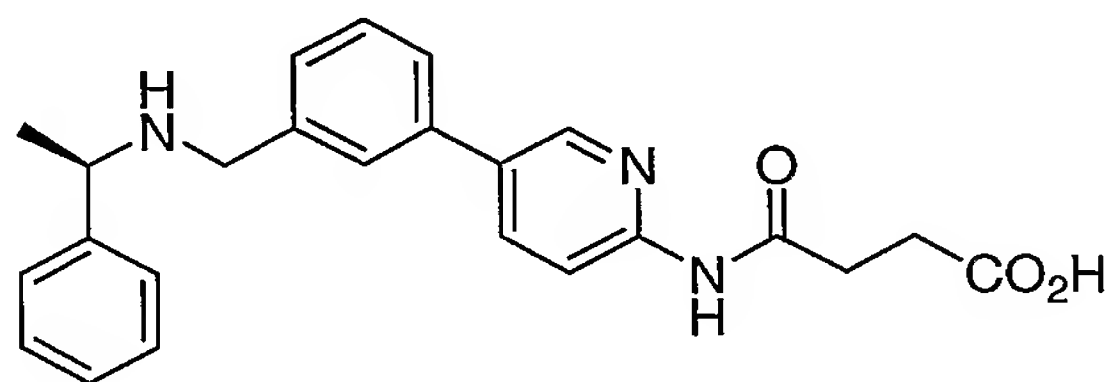
MW 381.426  
Mass found: 352, 393

20

**Example 149**

4-oxo-4-((5-(3-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)amino)butanoic acid

25



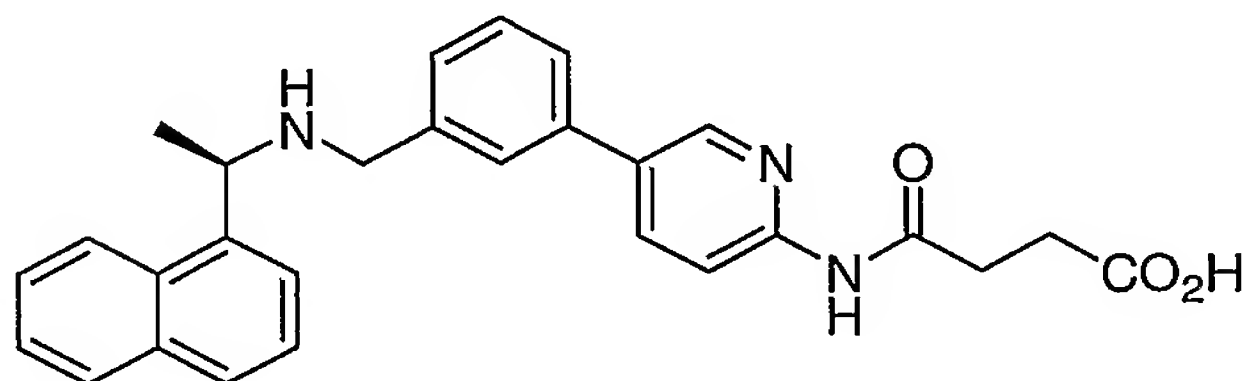
MW 403.479  
Mass found: 404, 300

30

- 143 -

**Example 150**

5 4-((5-(3-(((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)amino)-4-oxobutanoic acid



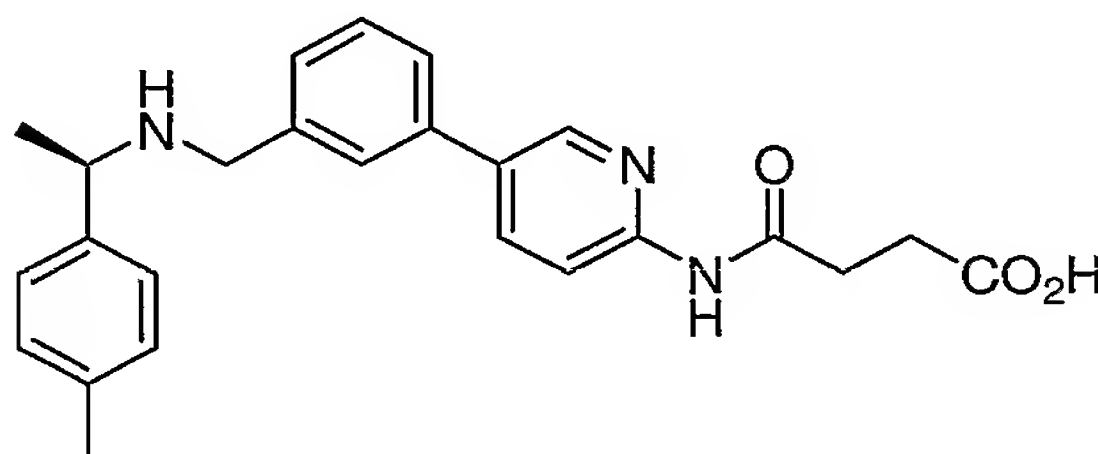
10

MW 453.539  
Mass found: 454, 300

**Example 151**

15

4-((5-(3-(((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)amino)-4-oxobutanoic acid



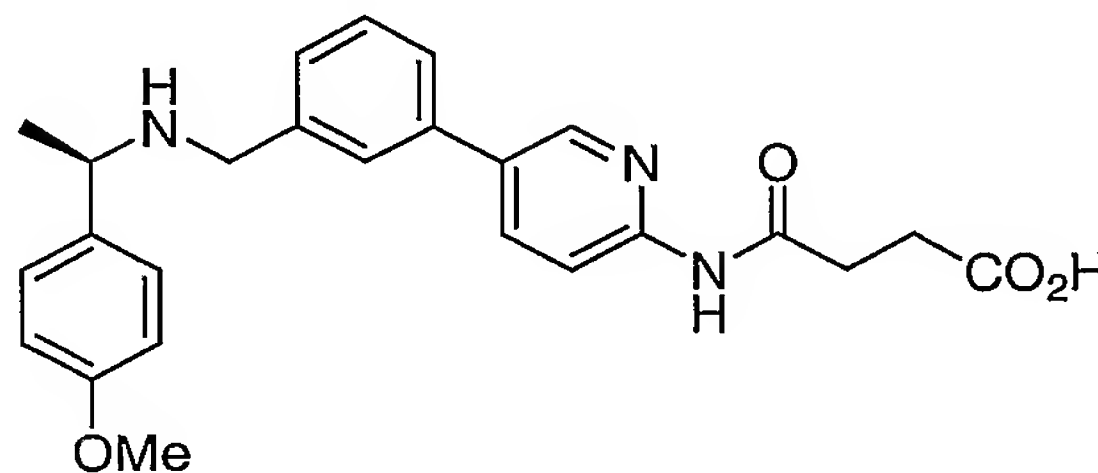
20

MW 417.506  
Mass found: 418, 300

**Example 152**

25

4-((5-(3-(((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)amino)-4-oxobutanoic acid



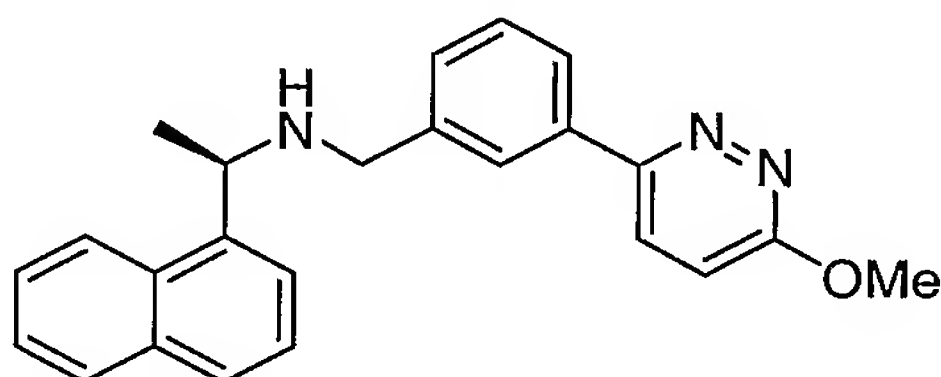
30

- 144 -

MW 433.505  
Mass found: 434, 300

**Example 153**

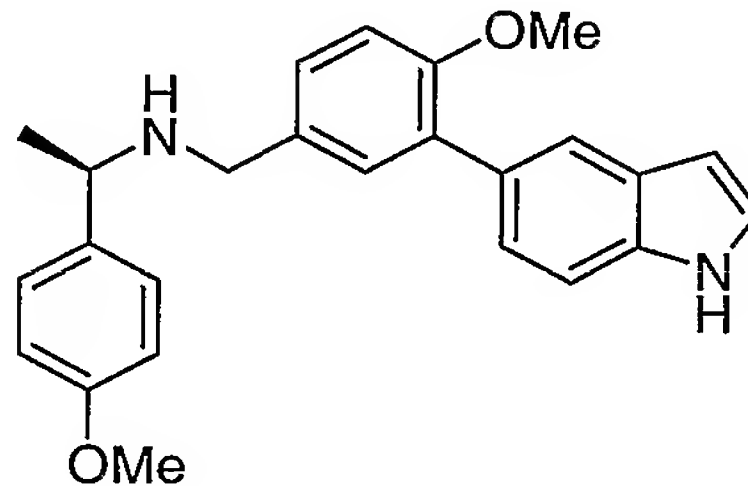
5 (1R)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



10 MW 369.466  
Mass found: 370, 739

**Example 154**

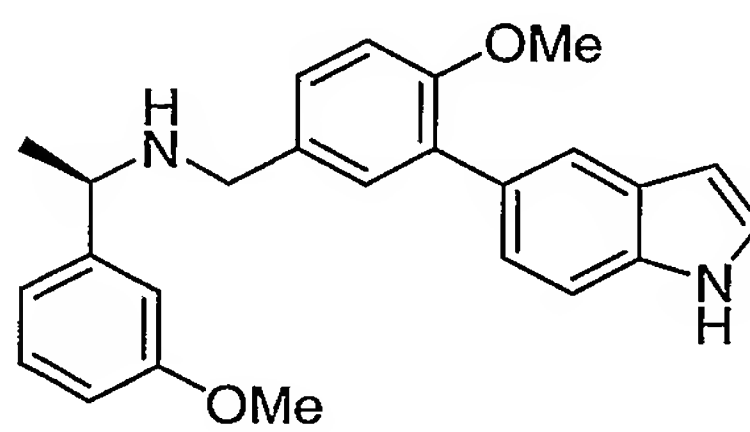
15 (1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



20 MW 386.492  
Mass found: 387, 773

**Example 155**

25 (1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



30



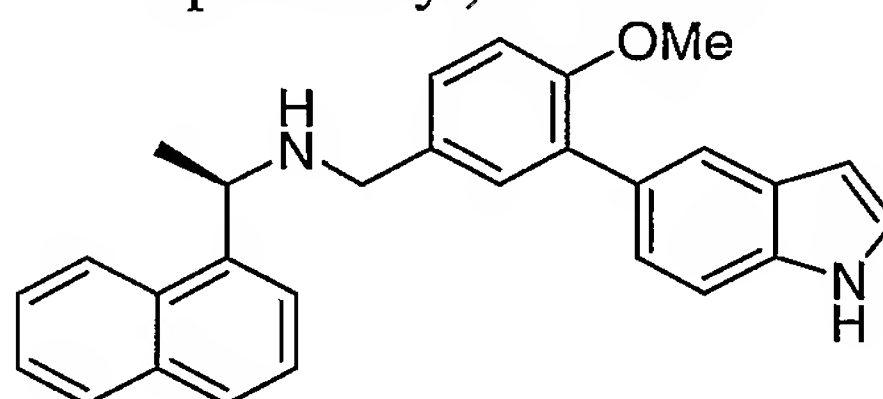
- 145 -

MW 386.492

Mass found: 387, 773

**Example 156**

5 (1R)-N-((3-(1H-indol-5-yl)-4-(methoxy)phenyl)methyl)-1-(2-naphthalenyl)ethanamine

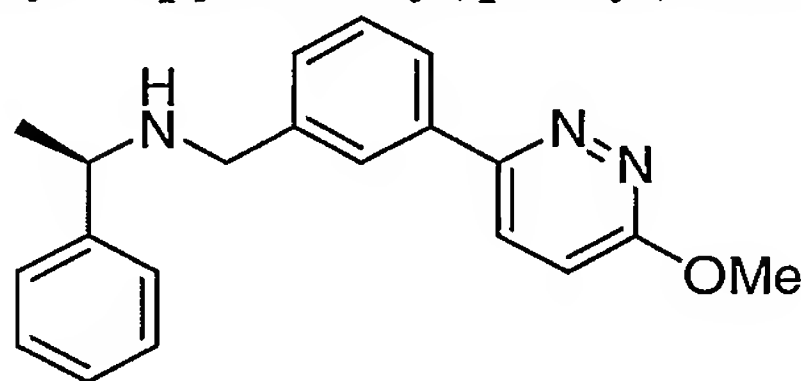


MW 406.526

Mass found: 371, 407, 326

**Example 157**

15 (1R)-N-((3-(6-(methoxy)-3-pyridazinyl)phenyl)methyl)-1-phenylethanamine

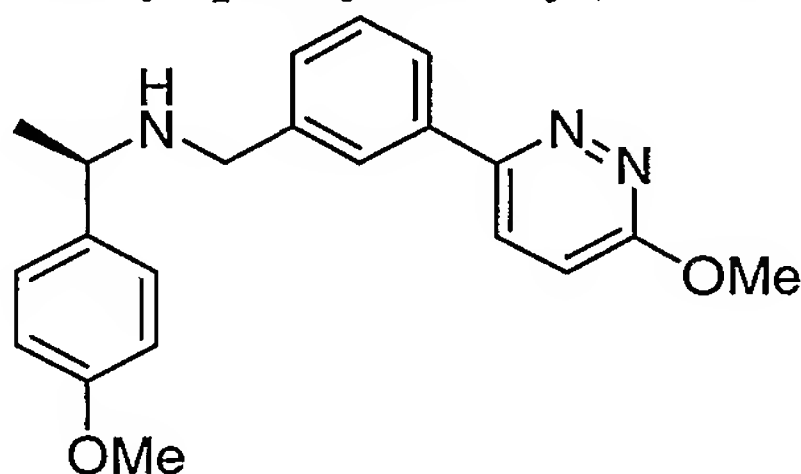


MW 319.406

Mass found: 320, 639

**Example 158**

25 (1R)-1-(4-(methoxy)phenyl)-N-((3-(6-(methoxy)-3-pyridazinyl)phenyl)methyl)ethanamine



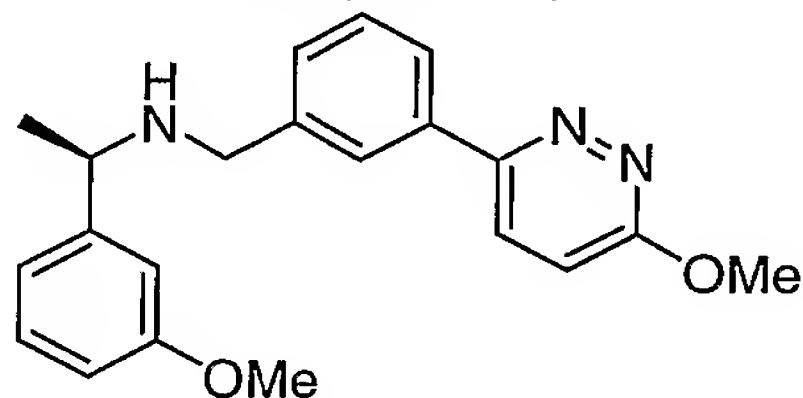
MW 349.432

Mass found: 350, 699

**Example 159**

- 146 -

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)ethanamine



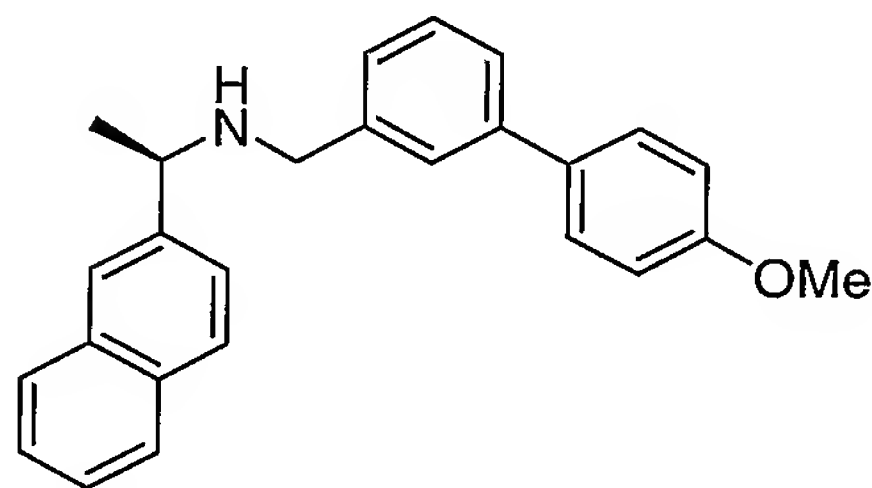
5

MW 349.432  
Mass found: 350, 699

10

**Example 160**

(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(2-naphthalenyl)ethanamine



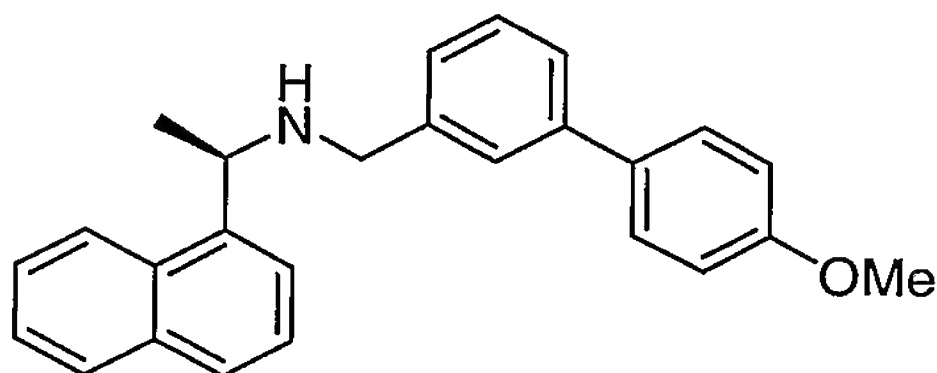
15

MW 367.49  
Mass found: 368

20

**Example 161**

(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



25

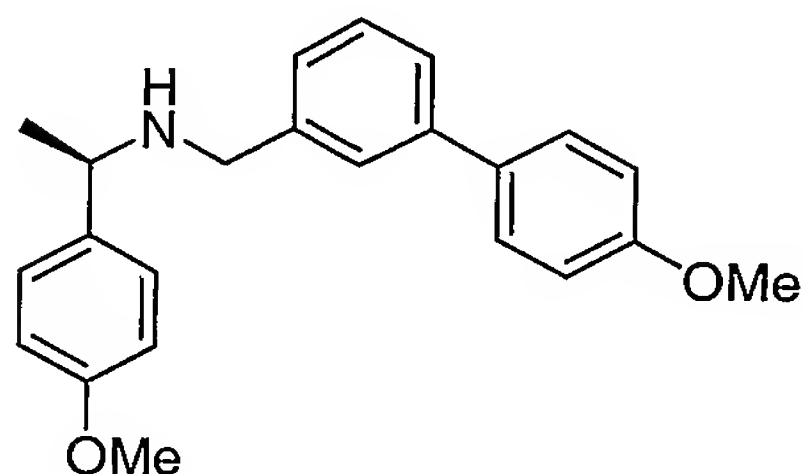
MW 367.49  
Mass found: 368, 735

30

**Example 162**

- 147 -

(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



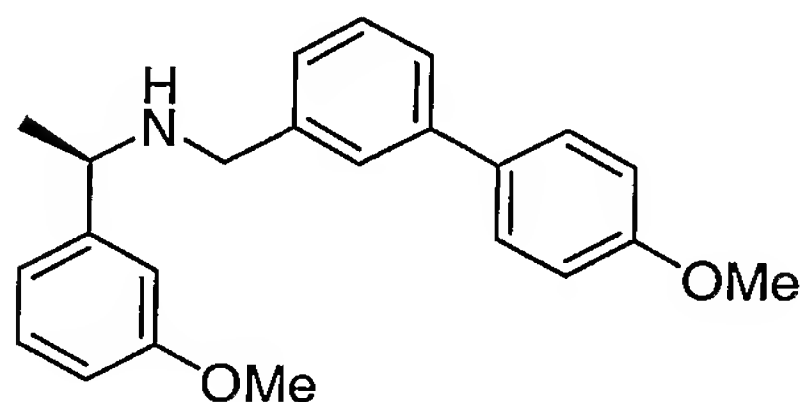
5

MW 347.456  
Mass found: 348, 695

10

**Example 163**

(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



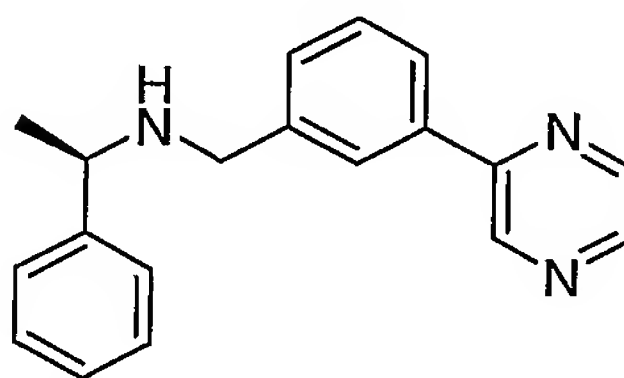
15

MW 347.456  
Mass found: 348, 695

20

**Example 164**

(1R)-1-phenyl-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine



25

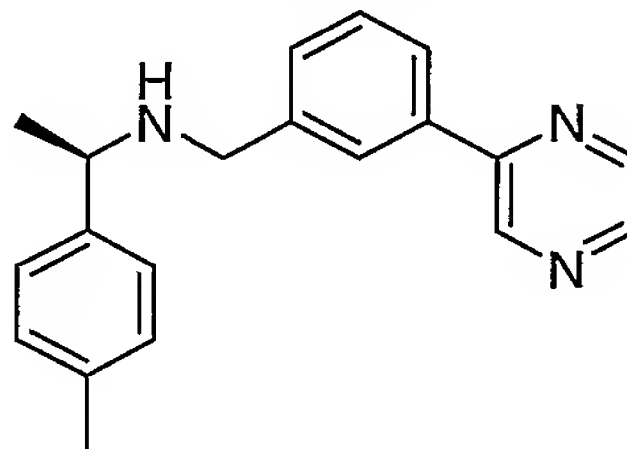
MW 289.38  
Mass found: 290, 579, 693

30

**Example 165**

- 148 -

(1R)-1-(4-methylphenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine



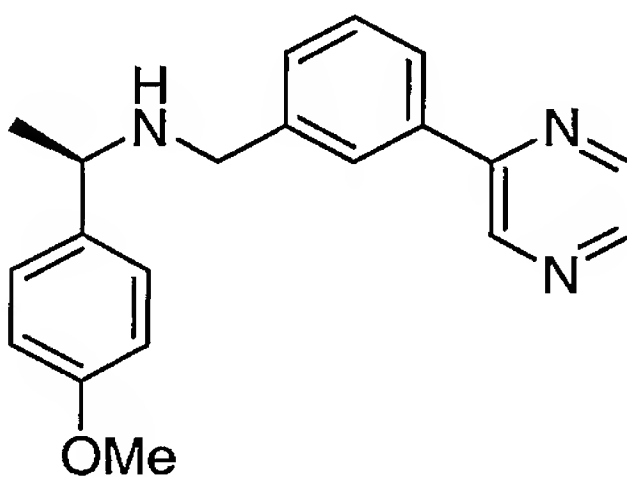
MW 303.407

Mass found: 304, 607, 721

5

**Example 166**

10 (1R)-1-(4-(methyloxy)phenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine



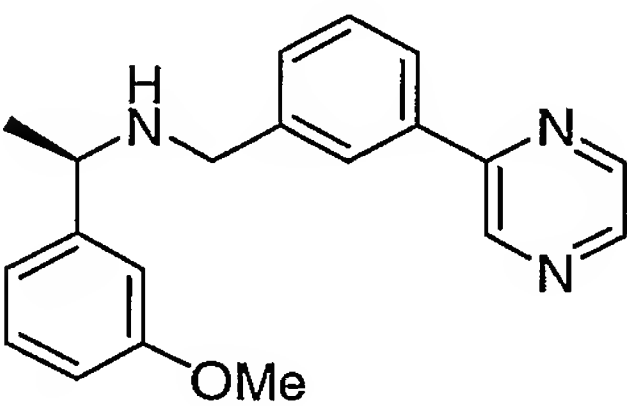
MW 319.406

Mass found: 320, 639, 753

15

**Example 167**

20 (1R)-1-(3-(methyloxy)phenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine



MW 319.406

Mass found: 320, 639, 753

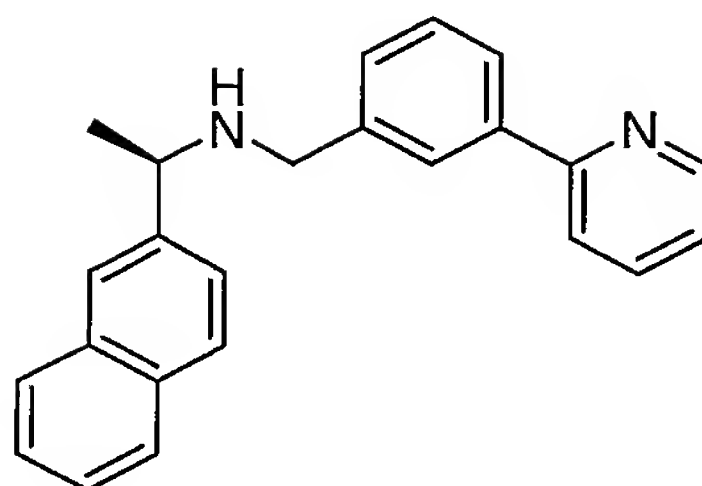
25

**Example 168**

30

(1R)-1-(2-naphthalenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine

- 149 -

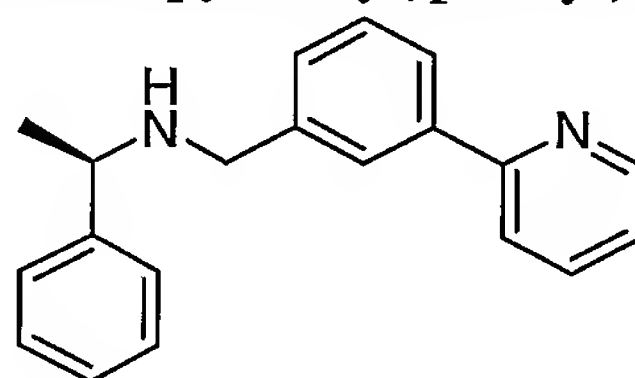


MW 338.452  
Mass found: 339, 677

5

**Example 169**

(1R)-1-phenyl-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine



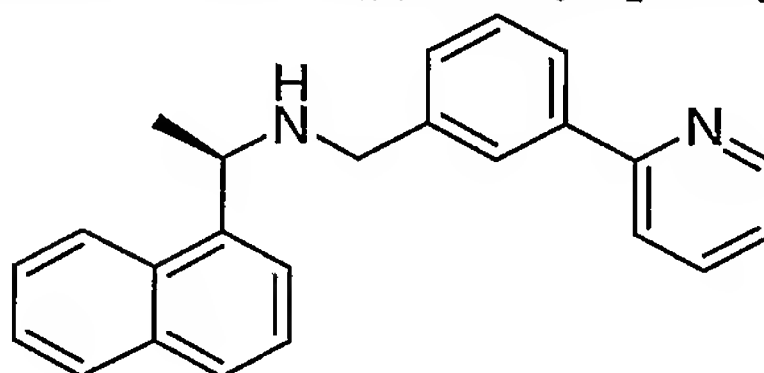
MW 288.392  
Mass found: 289, 577

10

15

**Example 170**

(1R)-1-(1-naphthalenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine



MW 338.452  
Mass found: 339, 677

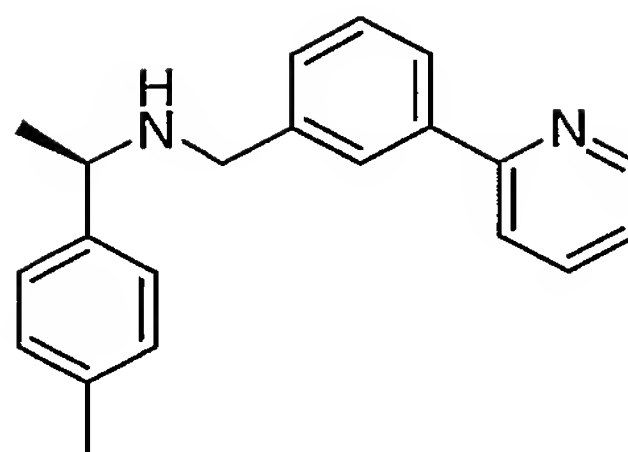
20

25

**Example 171**

(1R)-1-(4-methylphenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine

- 150 -



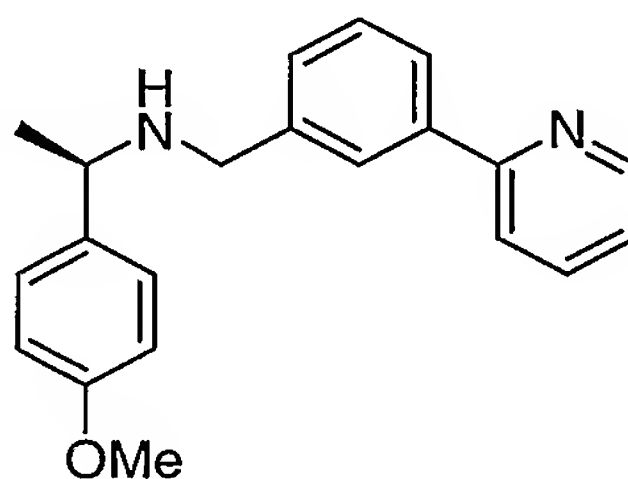
MW 302.419  
Mass found: 303, 605

5

**Example 172**

(1R)-1-(4-(methyloxy)phenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine

10

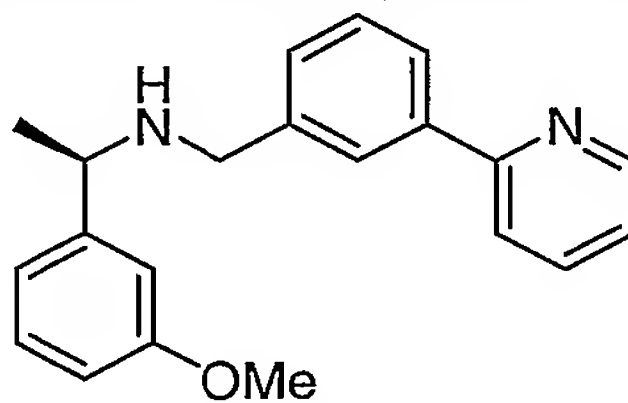


MW 318.418  
Mass found: 319, 637

15

**Example 173**

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine



MW 318.418  
Mass found: 319, 637

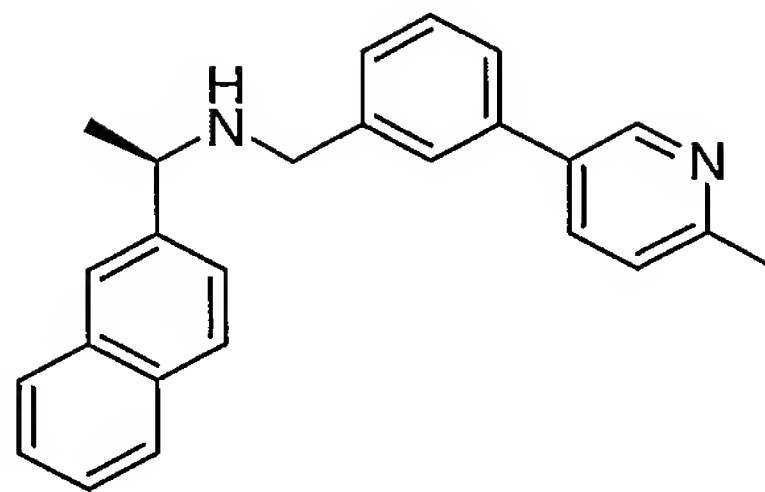
25

**Example 174**

(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine

30

- 151 -

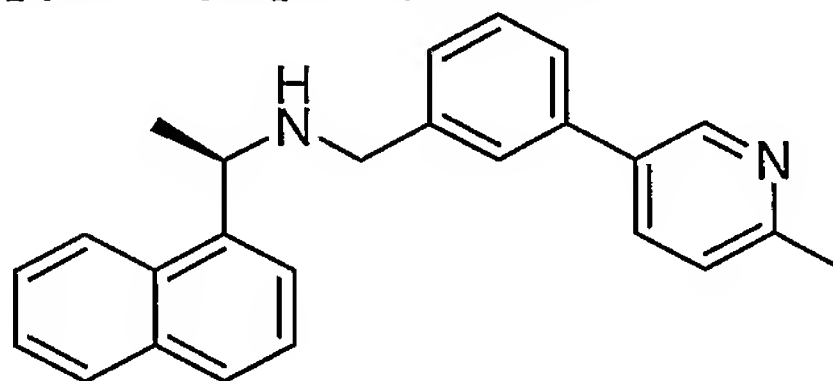


MW 352.479  
Mass found: 353, 705

5

**Example 175**

(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



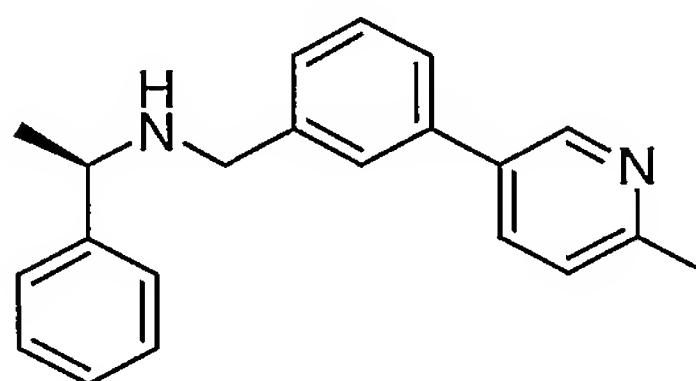
10

MW 352.479  
Mass found: 353, 705

15

**Example 176**

(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-phenylethanamine



20

MW 302.419  
Mass found: 303, 719

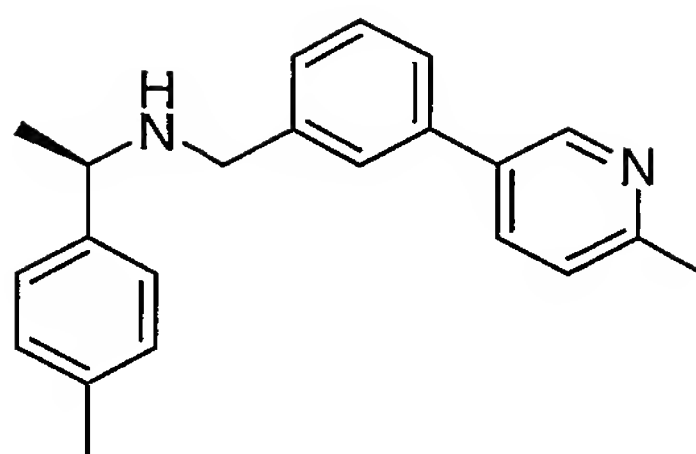
25

**Example 177**

(1R)-1-(4-methylphenyl)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)ethanamine



- 152 -



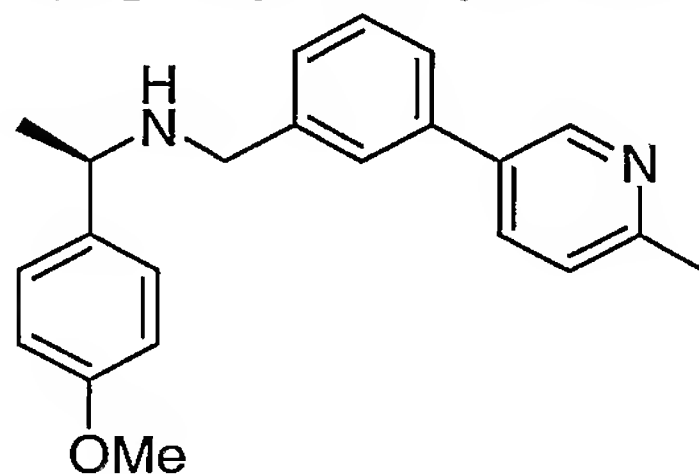
MW 316.446  
Mass found: 317, 747

5

**Example 178**

(1R)-1-(4-(methyloxy)phenyl)-N-((3-(6-methyl-3-yrindinyl)phenyl)methyl)ethanamine

10



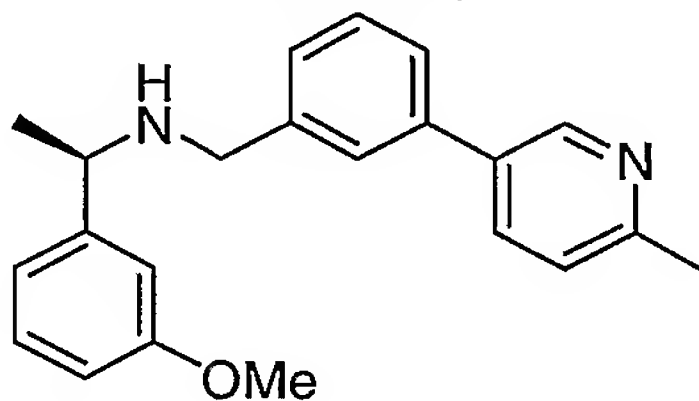
MW 332.445  
Mass found: 333, 779, 665

15

**Example 179**

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(6-methyl-3-yrindinyl)phenyl)methyl)ethanamine

20



MW 332.445  
Mass found: 333, 779, 665

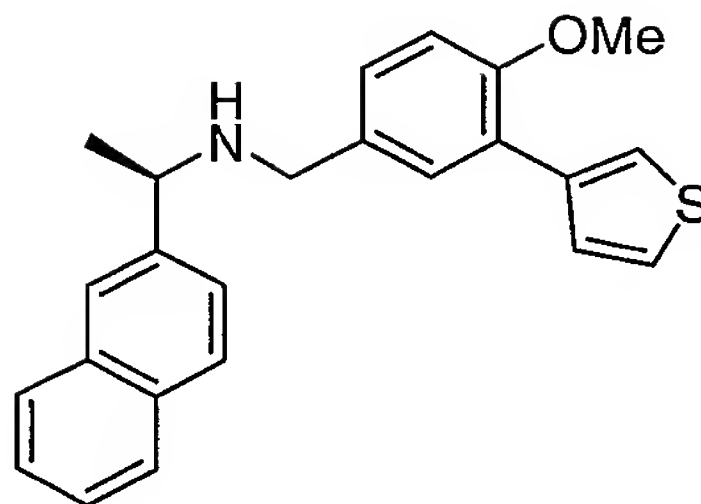
25

**Example 180**

(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine

30

- 153 -



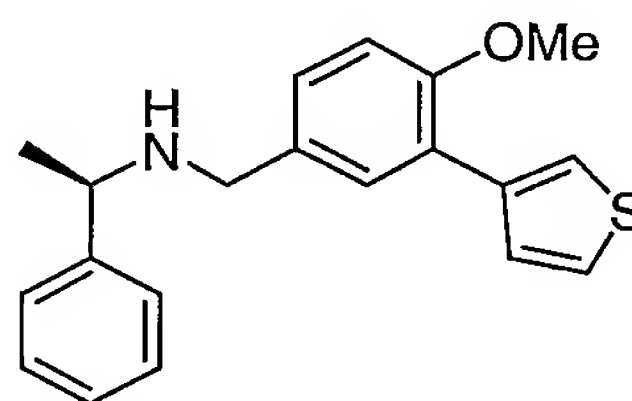
MW 373.518  
Mass found: 374, 747

5

**Example 181**

(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-phenylethanamine

10



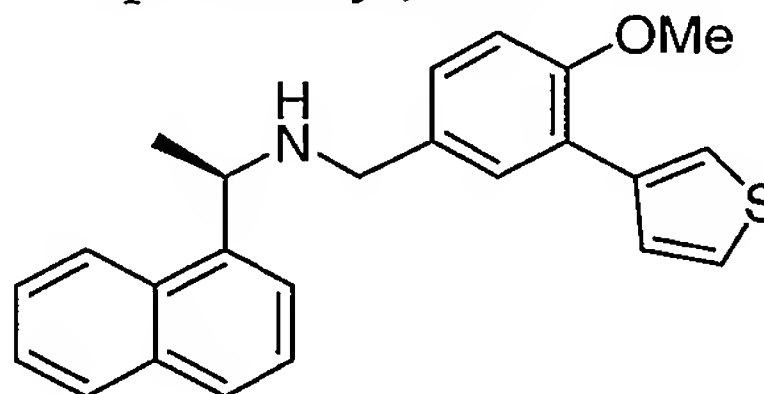
MW 323.458  
Mass found: 324, 647, 761

15

**Example 182**

(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

20



MW 373.518  
Mass found: 374, 747

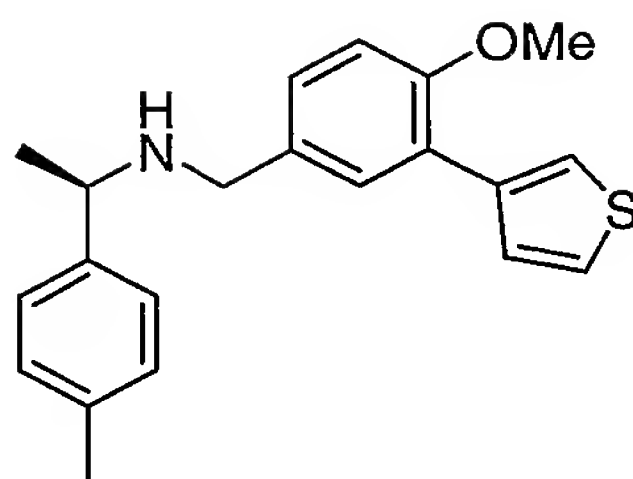
25

**Example 183**

(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine

30

- 154 -



MW 337.485

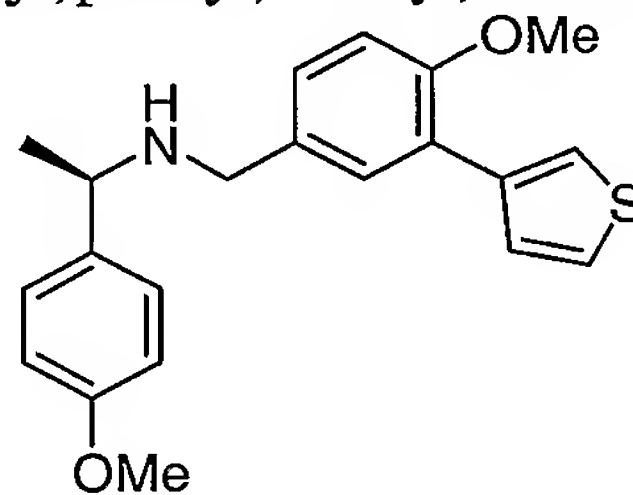
Mass found: 338, 675

5

**Example 184**

(1R)-1-(4-(methoxy)phenyl)-N-((4-(methoxy)-3-(3-thienyl)phenyl)methyl)ethanamine

10



MW 353.484

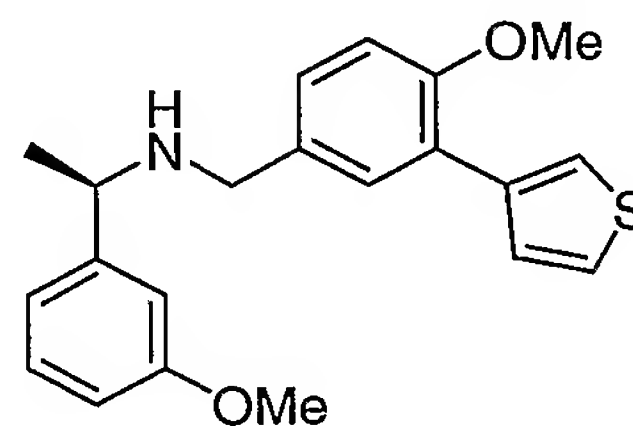
Mass found: 354, 707

15

**Example 185**

(1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(3-thienyl)phenyl)methyl)ethanamine

20



MW 353.484

Mass found: 354, 707

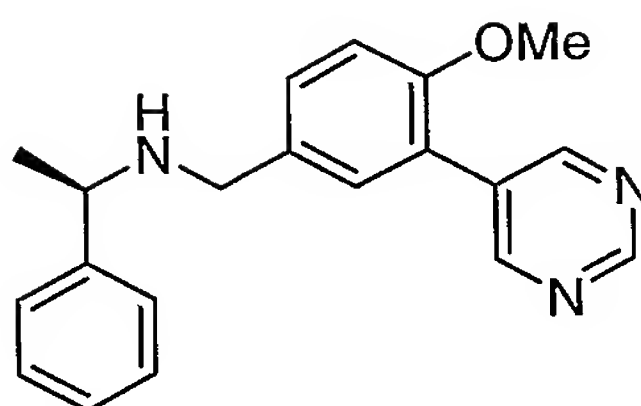
25

**Example 186**

(1R)-N-((4-(methoxy)-3-(5-pyrimidinyl)phenyl)methyl)-1-phenylethanamine

30

- 155 -



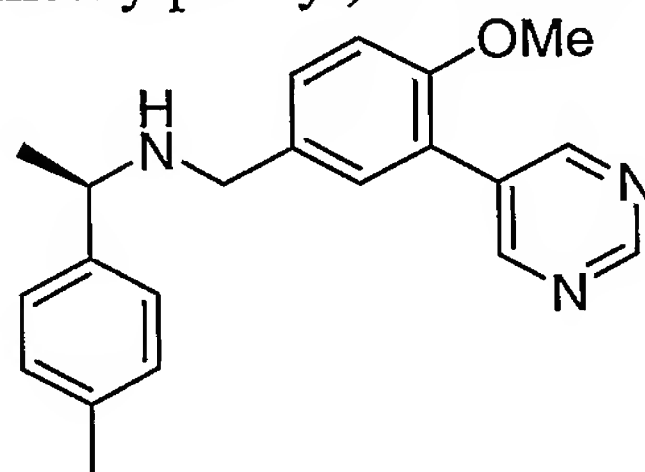
MW 319.406  
Mass found: 320, 361, 753

5

**Example 187**

(1R)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine

10



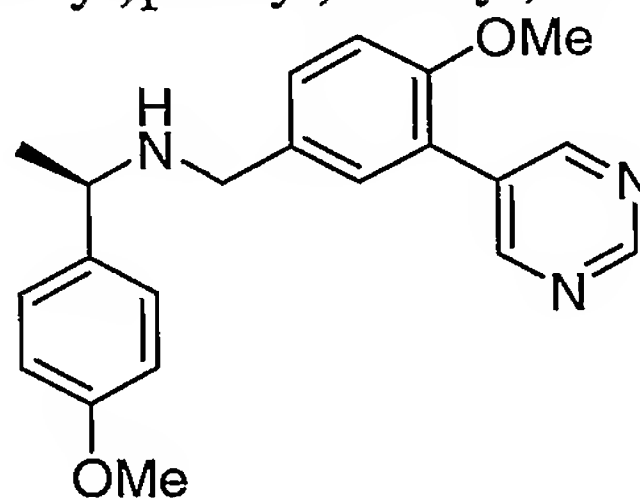
MW 333.433  
Mass found: 334, 781

15

**Example 188**

(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)ethanamine

20



MW 349.432  
Mass found: 350, 699

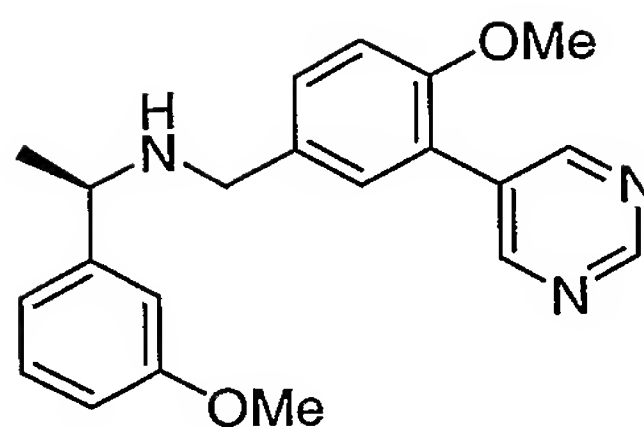
25

**Example 189**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)ethanamine

30

- 156 -



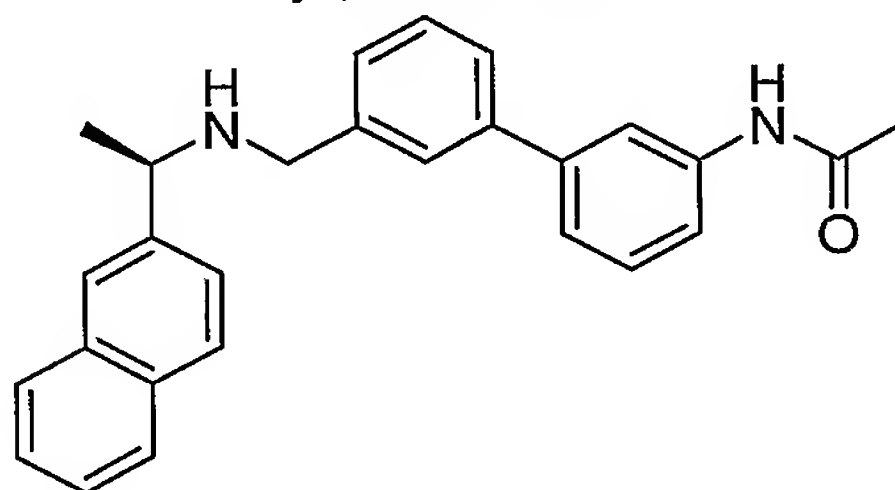
MW 349.432  
Mass found: 350, 699

5

**Example 190**

N-(3'-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

10



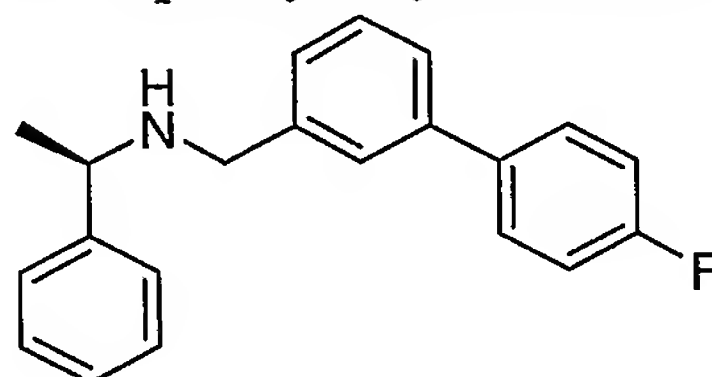
MW 394.515  
Mass found: 395, 789

15

**Example 191**

(1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

20



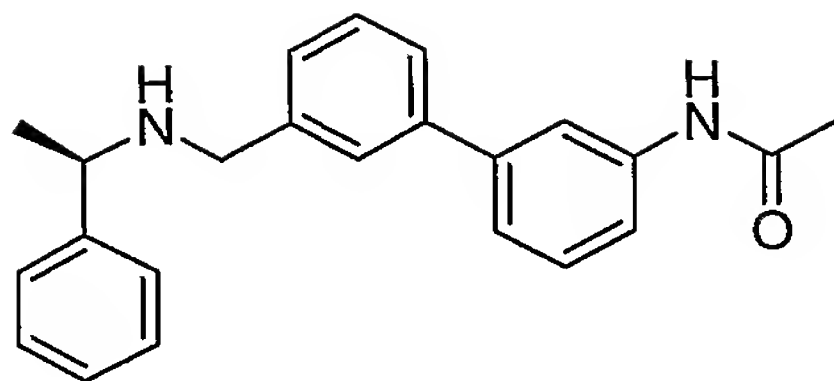
MW 305.394  
Mass found: 306, 202, 243

25

**Example 192**

N-(3'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

- 157 -



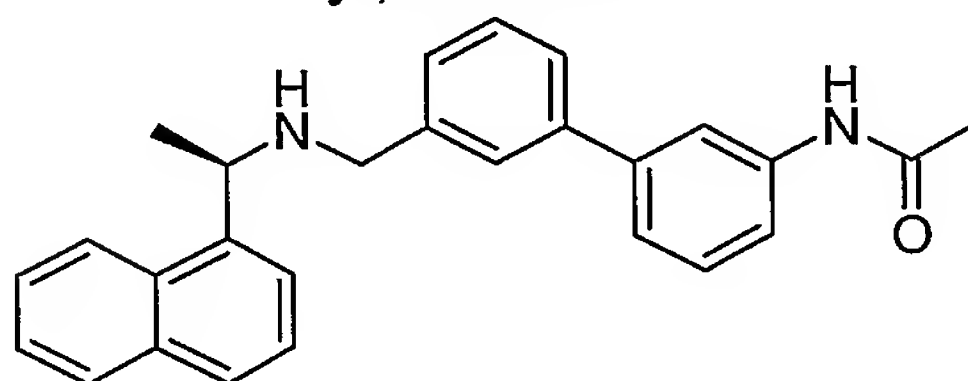
MW 344.456  
Mass found: 345, 689

5

**Example 193**

N-(3'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

10



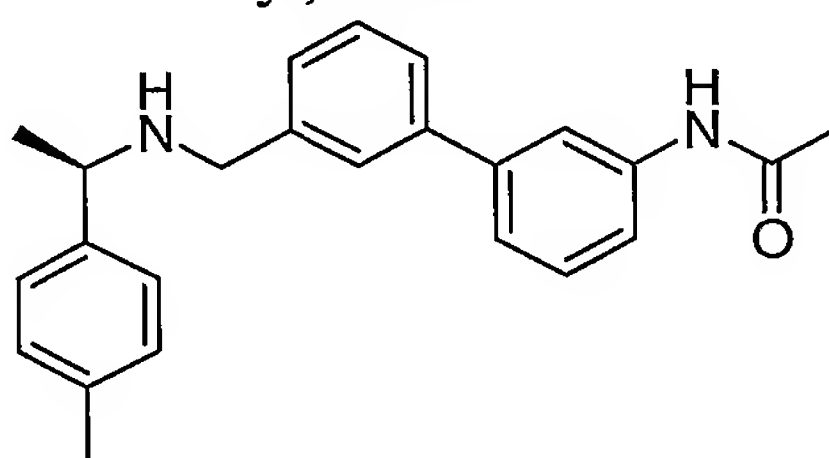
MW 394.515  
Mass found: 395, 789

15

**Example 194**

N-(3'-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

20



MW 358.482  
Mass found: 359, 717

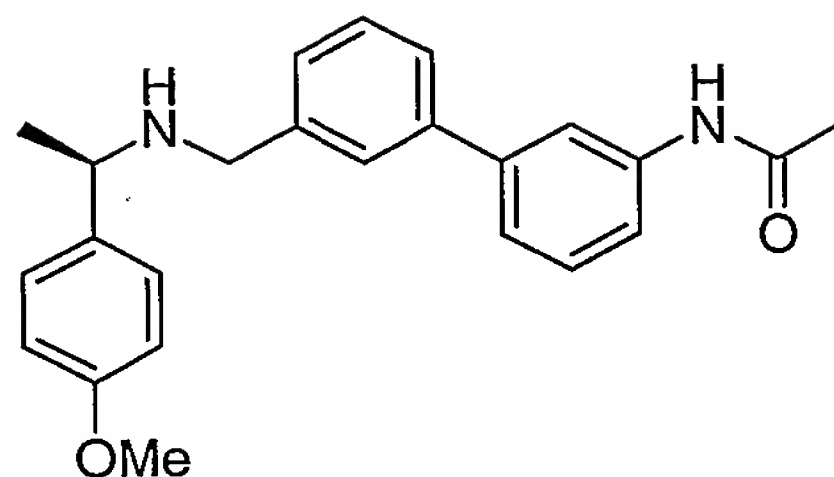
25

**Example 195**

N-(3'-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

30

- 158 -



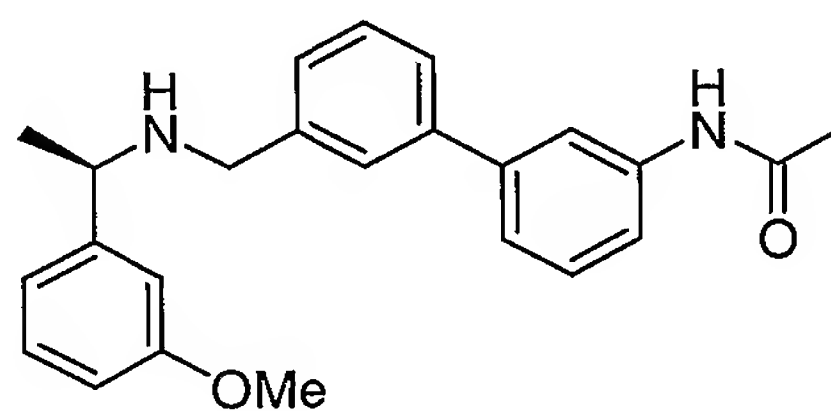
MW 374.481  
Mass found: 375, 749

5

**Example 196**

N-(3'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

10

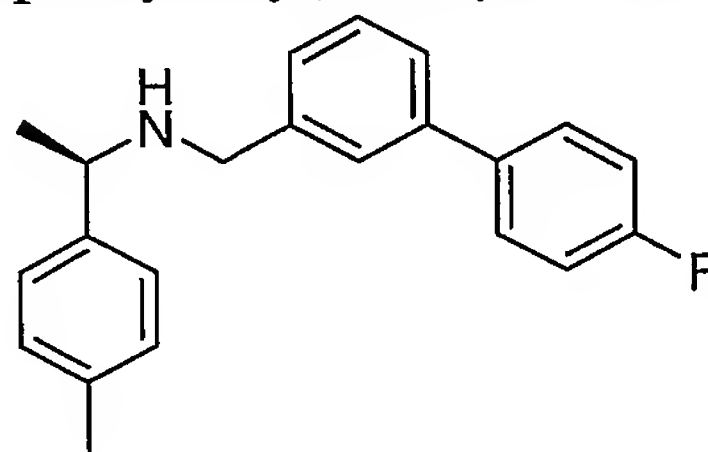


MW 374.481  
Mass found: 375, 749, 416

15

**Example 197**

(1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



MW 319.421  
Mass found: 320, 202, 243

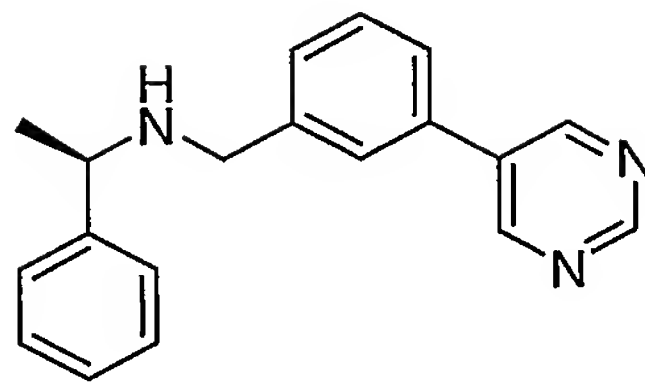
20

**Example 198**

(1R)-1-phenyl-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine

25

- 159 -



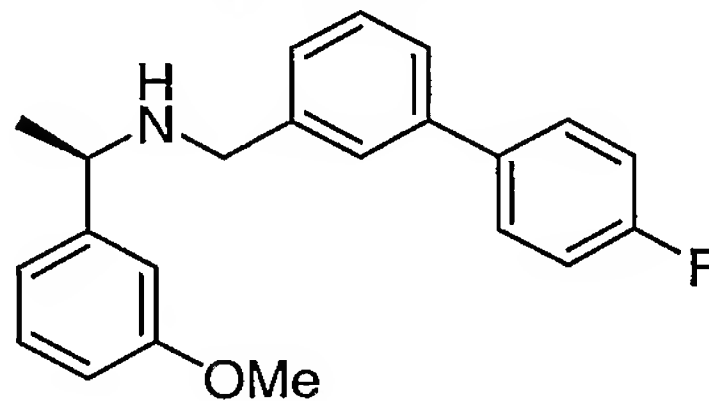
MW 289.38  
Mass found: 290, 693, 331

5

**Example 199**

(1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10

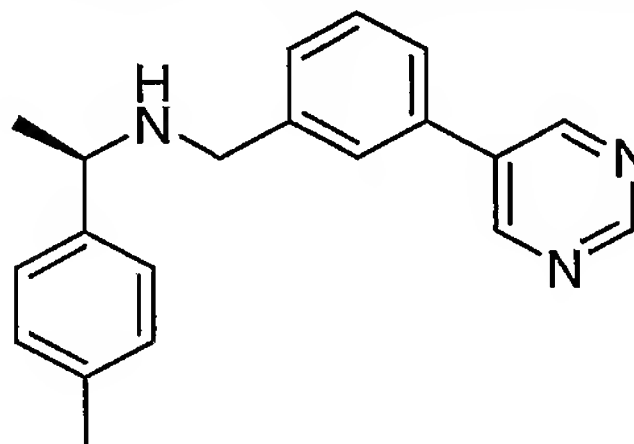


MW 335.42  
Mass found: 336, 202, 243

15

**Example 200**

(1R)-1-(4-methylphenyl)-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine



20

MW 303.407  
Mass found: 304, 721, 345

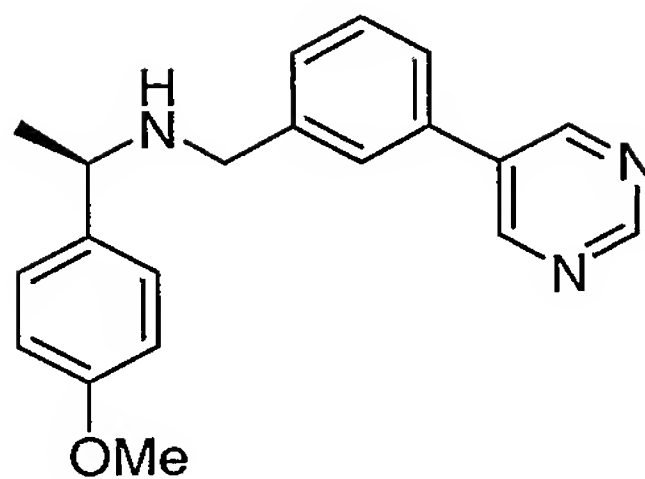
25

**Example 201**

(1R)-1-(4-(methyloxy)phenyl)-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine



- 160 -



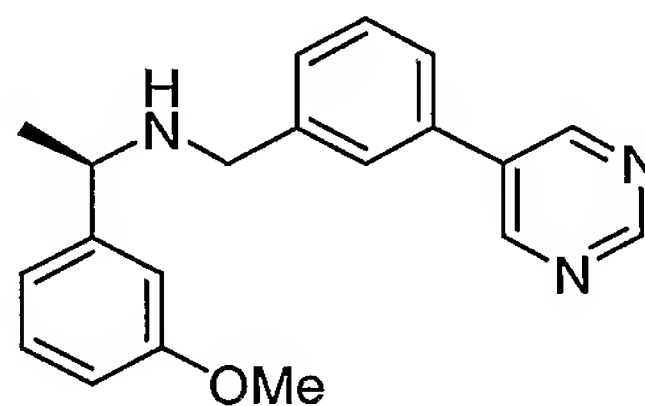
MW 319.406  
Mass found: 320, 753

5

**Example 202**

(1R)-1-(3-(methoxy)phenyl)-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine

10



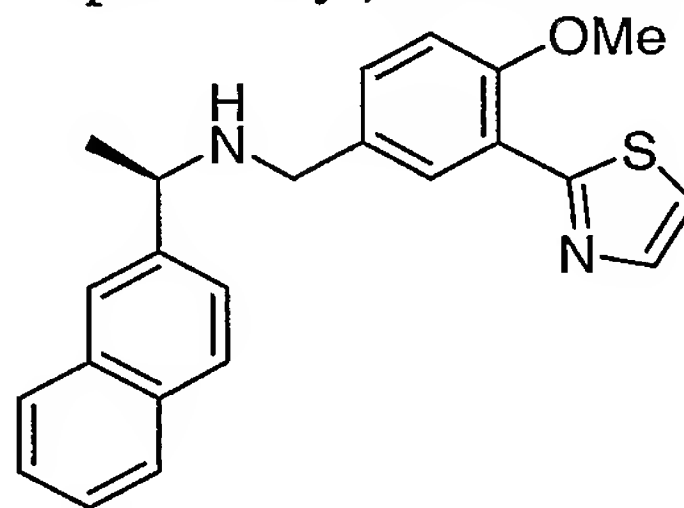
MW 319.406  
Mass found: 320, 753, 361

15

**Example 203**

(1R)-N-((4-(methoxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine

20



MW 374.506  
Mass found: 375, 749

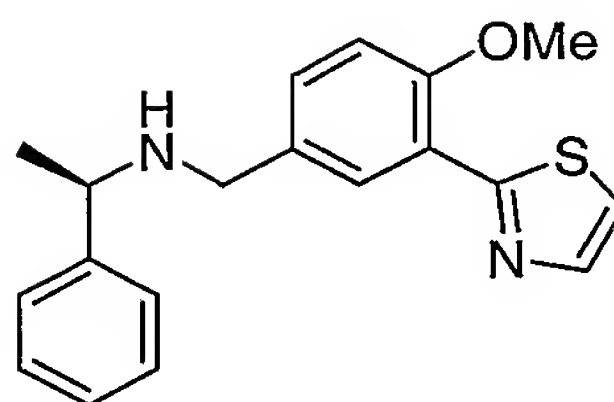
25

**Example 204**

(1R)-N-((4-(methoxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-phenylethanamine

30

- 161 -

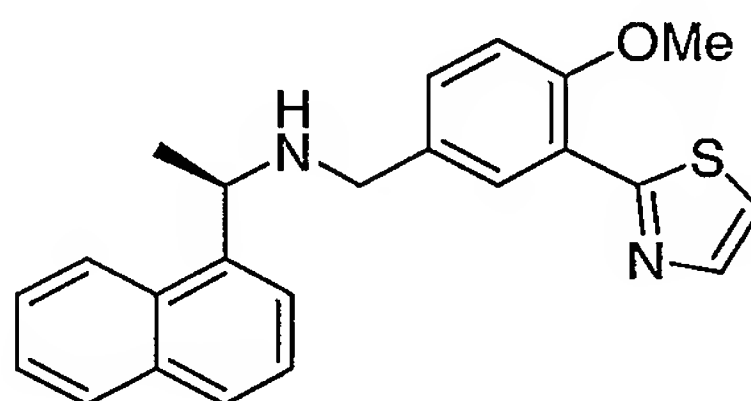


MW 324.446  
Mass found: 325, 649

5

**Example 205**

10 (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

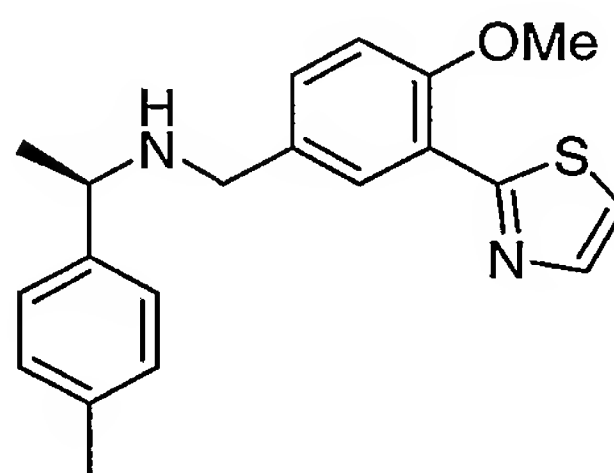


MW 374.506  
Mass found: 375, 749

15

**Example 206**

20 (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



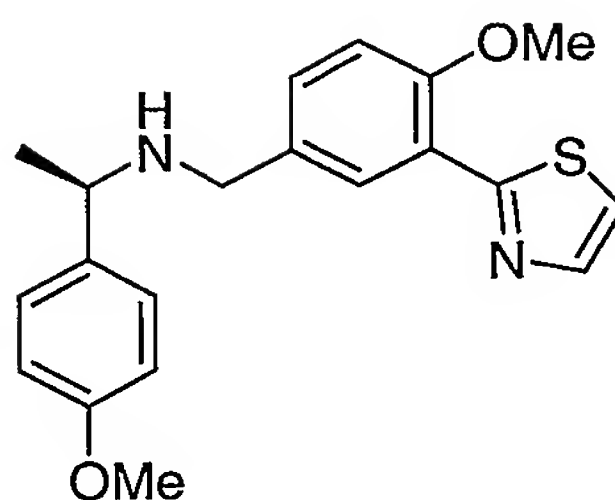
MW 338.473  
Mass found: 339, 677

25

**Example 207**

30 (1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine

- 162 -

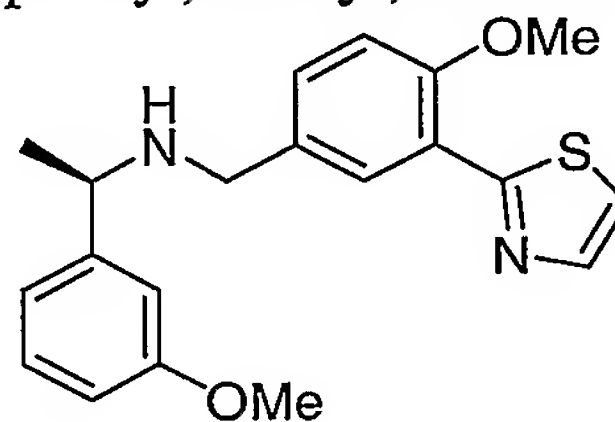


MW 354.472  
Mass found: 355, 709

5

**Example 208**

10 (1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine

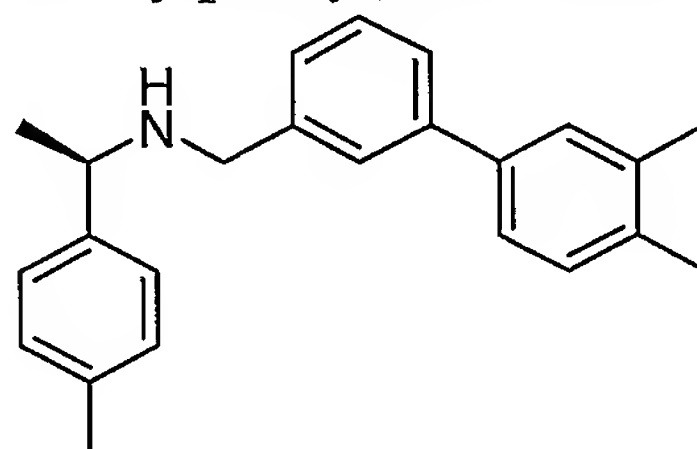


15

MW 354.472  
Mass found: 355, 709

**Example 209**

20 (1R)-N-((3',4'-dimethyl-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



25

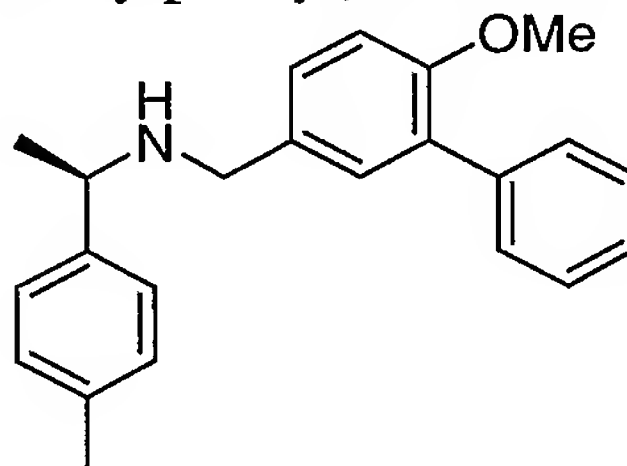
MW 329.484  
Mass found: 330, 195, 212

**Example 210**

30

- 163 -

(1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



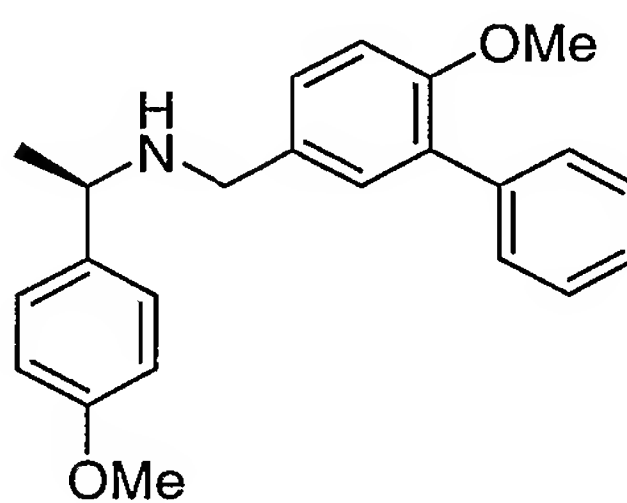
5

MW 331.457  
Mass found: 197, 332

### Example 211

10

(1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



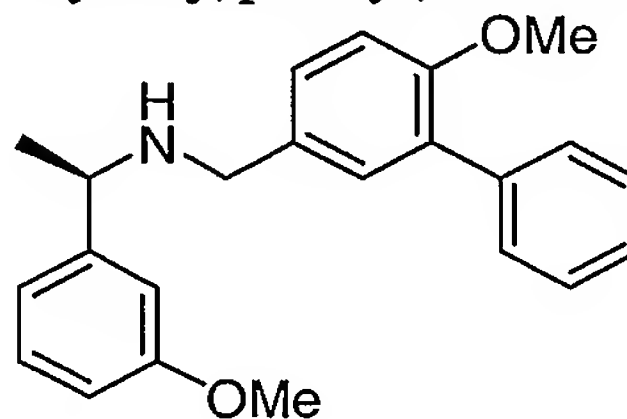
15

MW 347.456  
Mass found: 197, 348

### Example 212

20

(1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



25

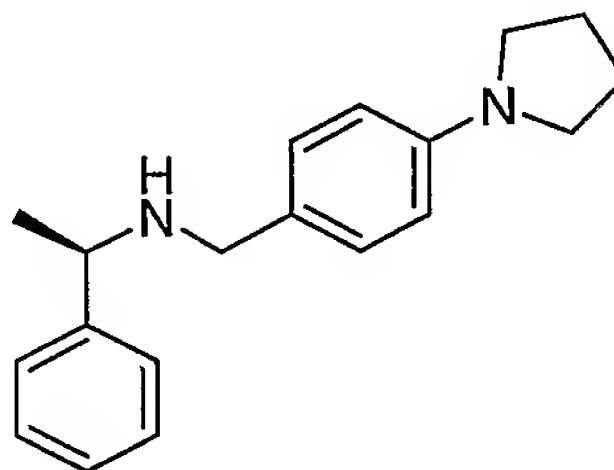
MW 347.456  
Mass found: 197, 348

### Example 213

30

- 164 -

(1R)-1-phenyl-N-((4-(1-pyrrolidinyl)phenyl)methyl)ethanamine



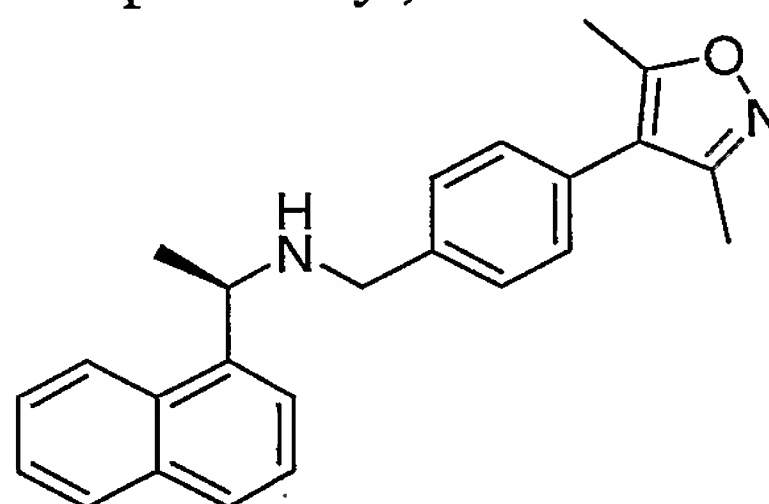
5

MW 280.413  
Mass found: 160, 561, 281

10

**Example 214**

(1R)-N-((4-(3,5-dimethyl-4-isoxazolyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



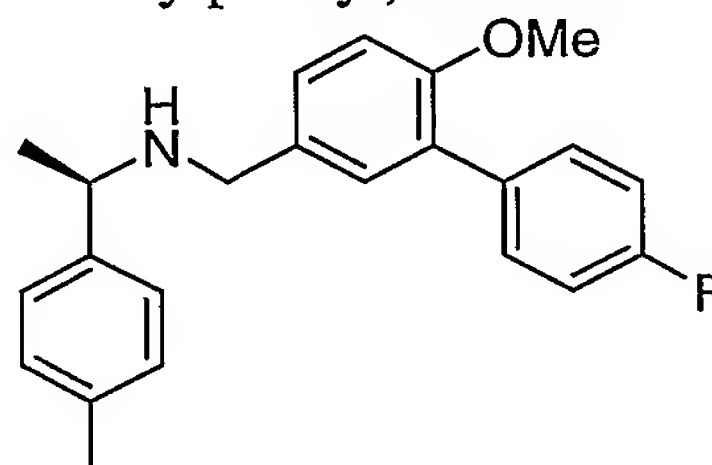
15

MW 356.467  
Mass found: 155, 357, 203

20

**Example 215**

(1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



25

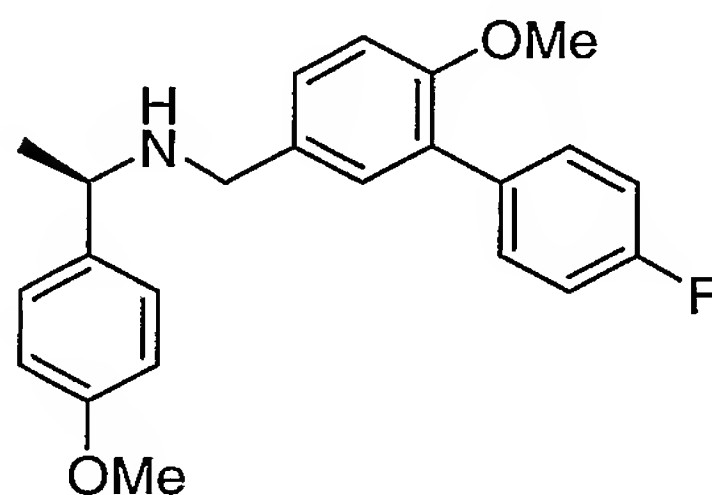
MW 349.447  
Mass found: 350

- 165 -

**Example 216**

(1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

5



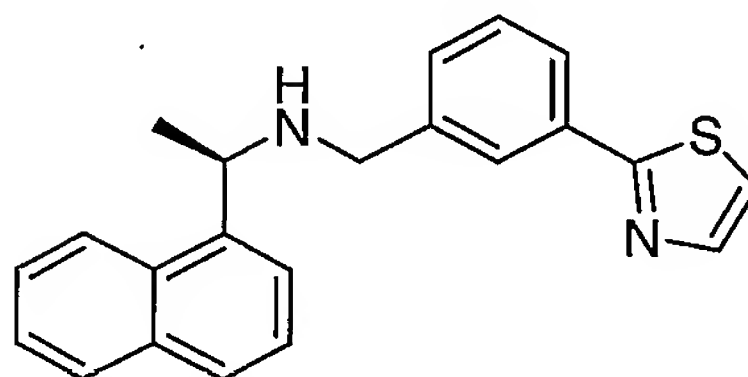
MW 365.446  
Mass found: 366

10

**Example 217**

(1R)-1-(1-naphthalenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine

15



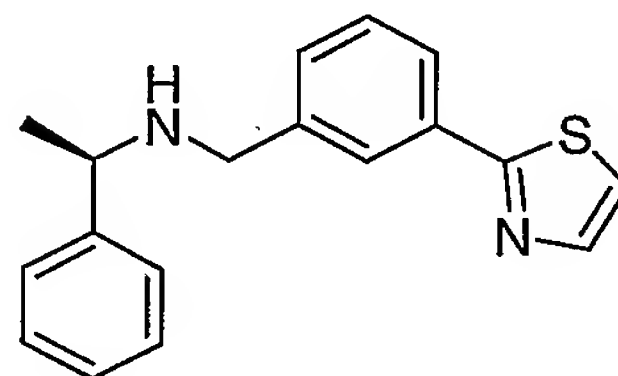
MW 344.48  
Mass found: 345, 689

20

**Example 218**

(1R)-1-phenyl-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine

25



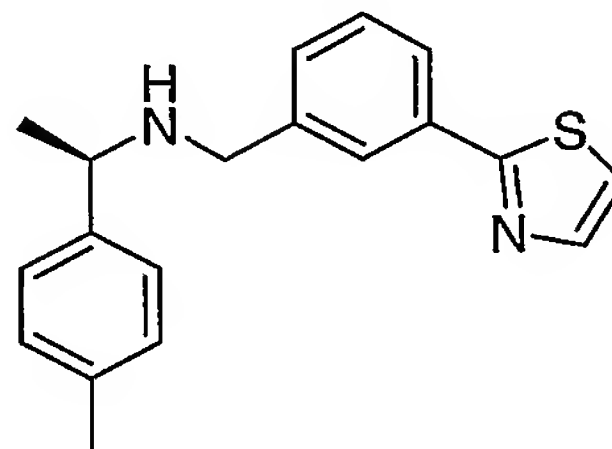
MW 294.42  
Mass found: 295, 589

30

**Example 219**

- 166 -

(1R)-1-(4-methylphenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine



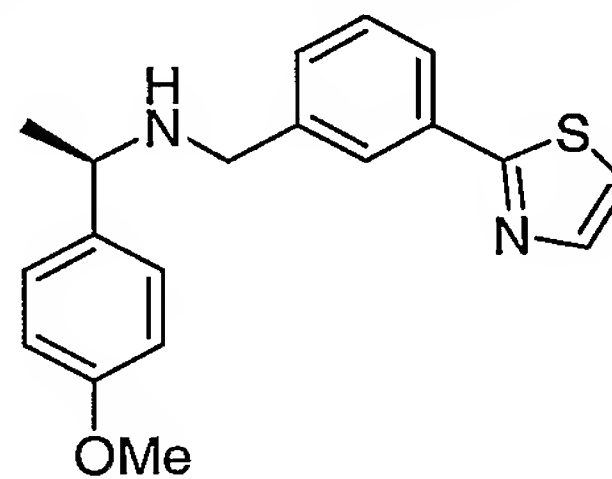
5

MW 303.407

Mass found: 304, 607

**Example 220**

10 (1R)-1-(4-(methyloxy)phenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine



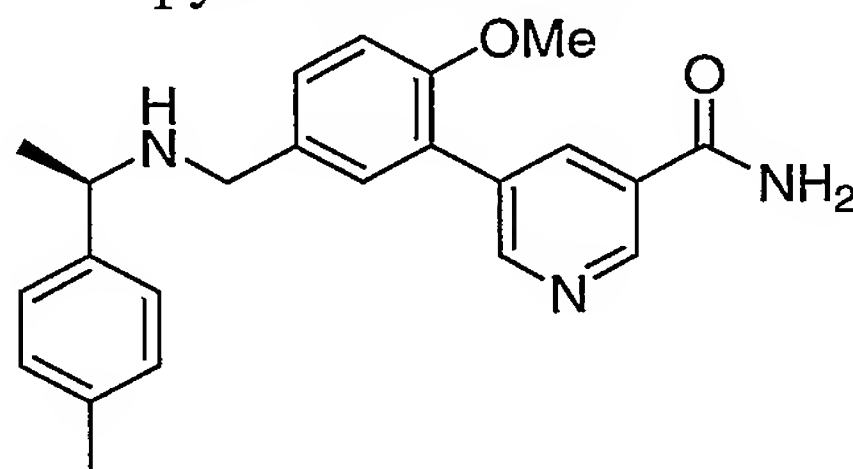
MW 324.446

Mass found: 325, 649

15

**Example 221**

20 5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



MW 375.47

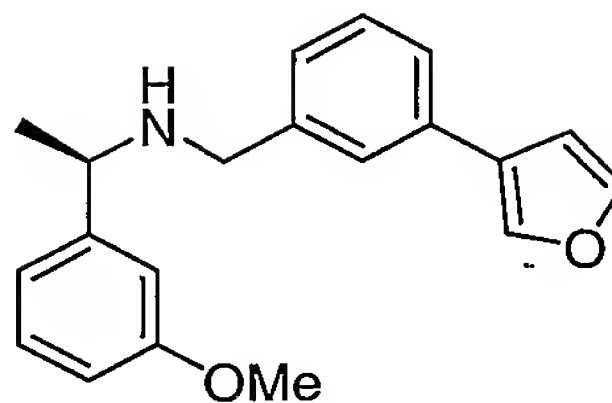
Mass found: 376, 417, 751, 865

25

**Example 222**

(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

- 167 -



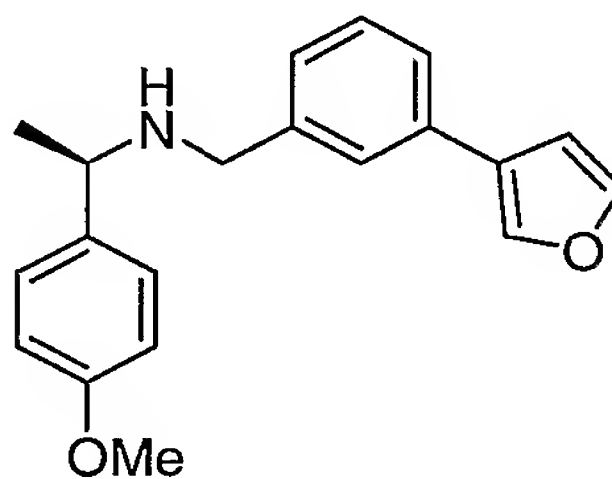
MW 307.391  
Mass found: 308, 615

5

**Example 223**

(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

10

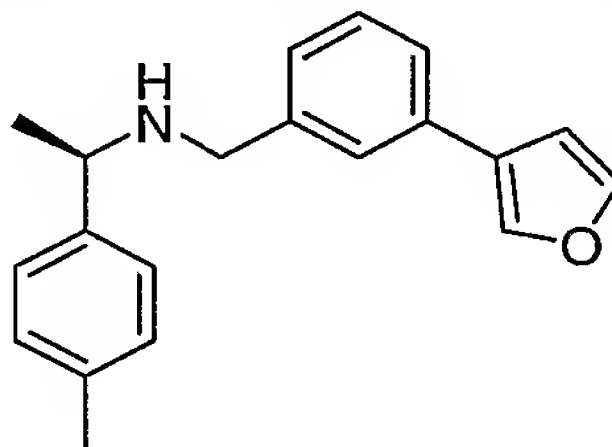


MW 307.391  
Mass found: 308, 615

15

**Example 224**

(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



MW 291.392  
Mass found: 292, 583

20

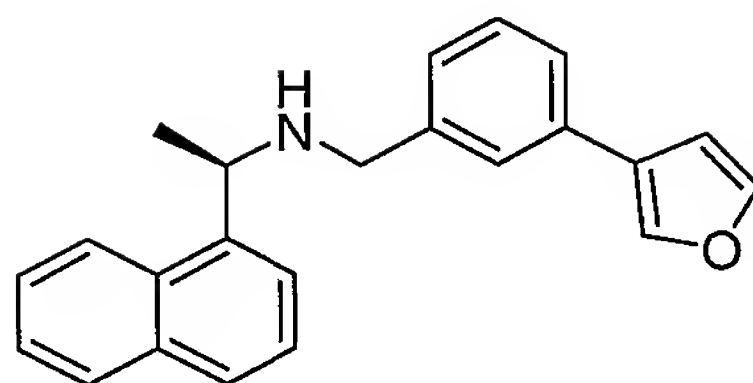
**Example 225**

(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

25



- 168 -

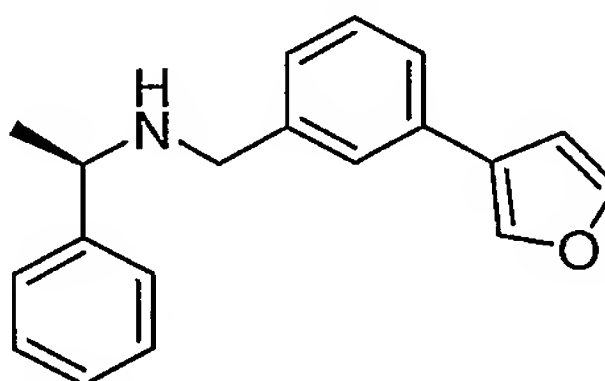


MW 327.425  
Mass found: 328, 655

5

**Example 226**

10 (1R)-N-((3-(3-furanyl)phenyl)methyl)-1-phenylethanamine

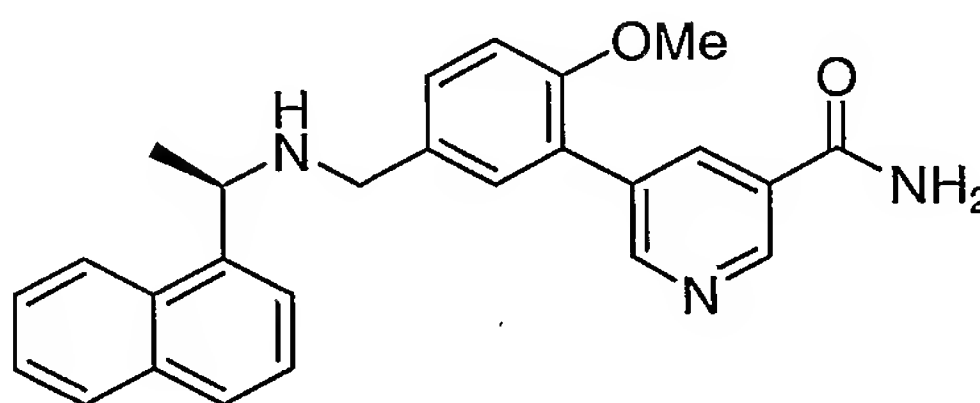


MW 277.365  
Mass found: 278, 555

15

**Example 227**

20 5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



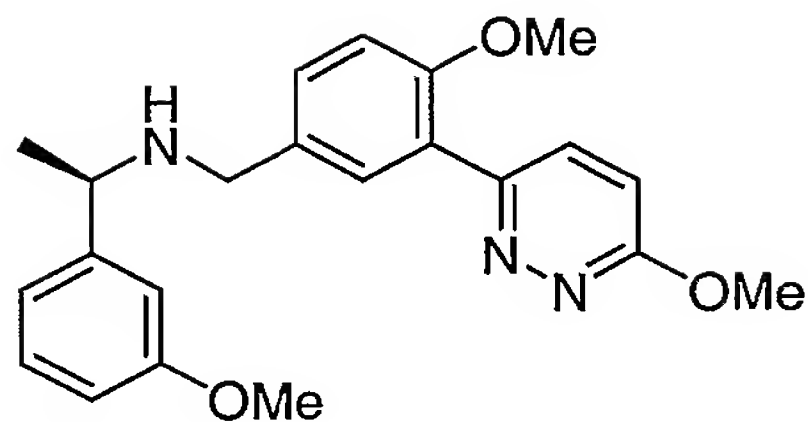
MW 411.503  
Mass found: 412, 823

25

**Example 228**

30 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

- 169 -

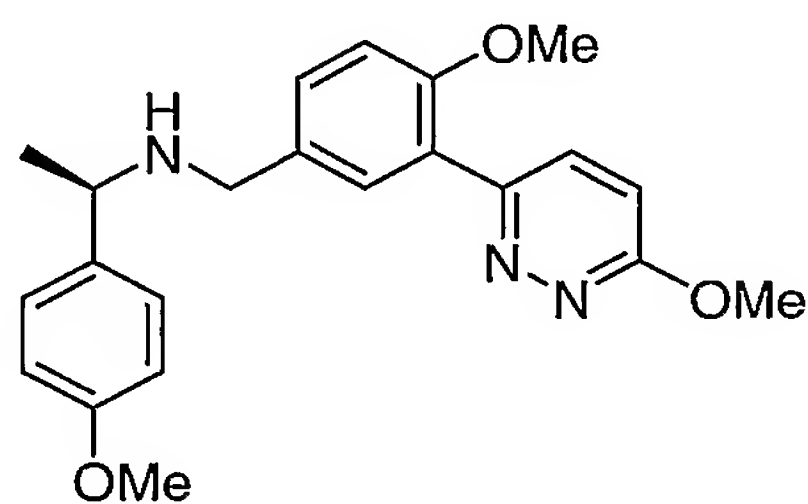


MW 379.457  
Mass found: 380, 759

5

**Example 229**

10 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



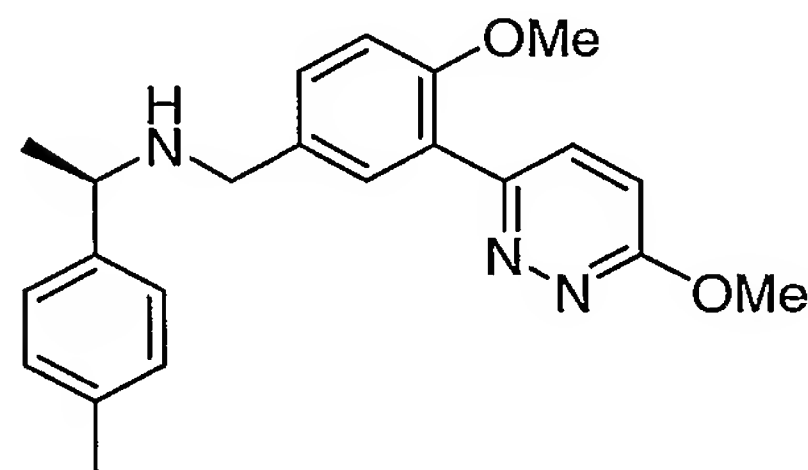
15

MW 379.457  
Mass found: 380, 759

**Example 230**

20

(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



25

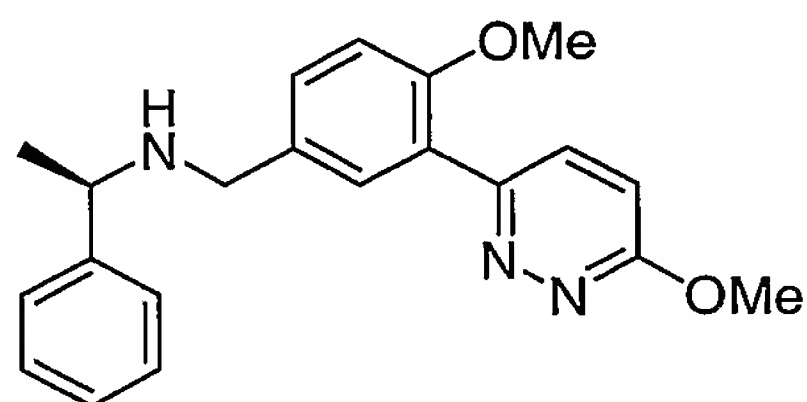
MW 363.458  
Mass found: 364, 727

30

**Example 231**

- 170 -

(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-phenylethanamine



5

MW 349.432

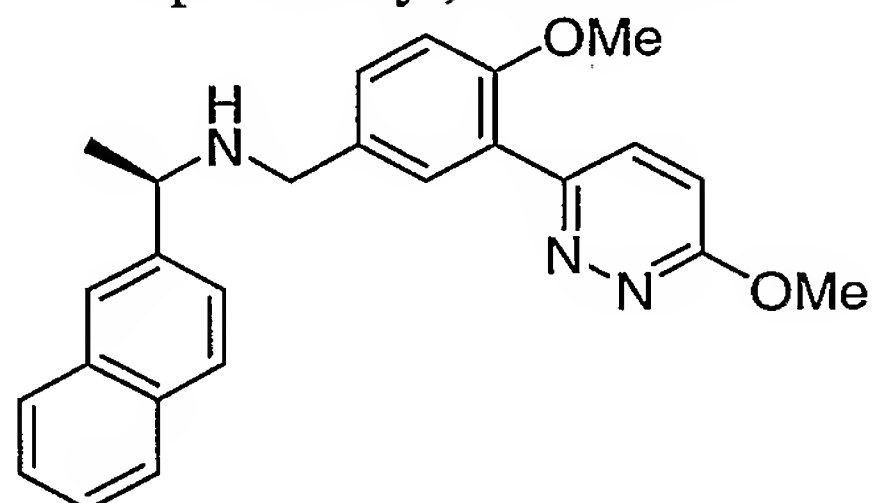
Mass found: 350, 699

10

**Example 232**

(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine

15



MW 399.491

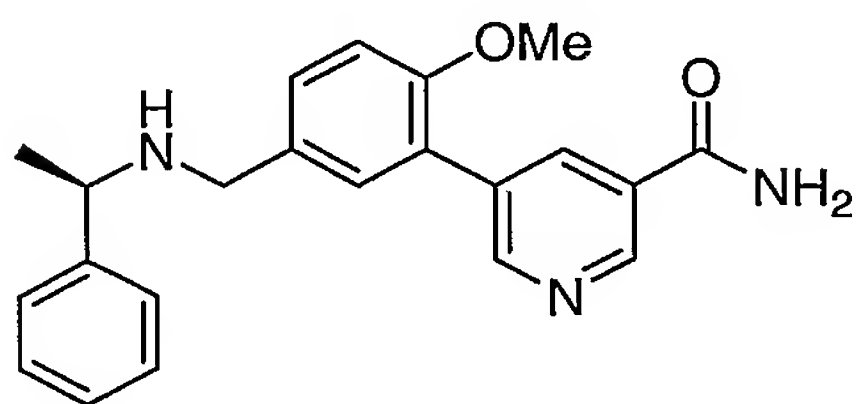
Mass found: 400, 799

20

**Example 233**

5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-3-pyridinecarboxamide

25



MW 361.443

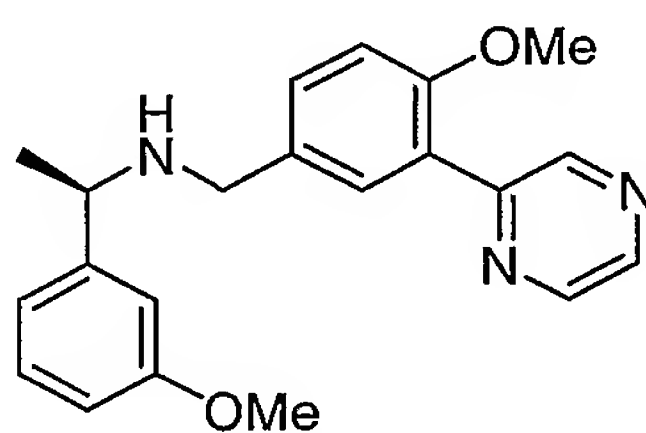
Mass found: 362, 403, 723, 837

30

- 171 -

**Example 234**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)ethanamine

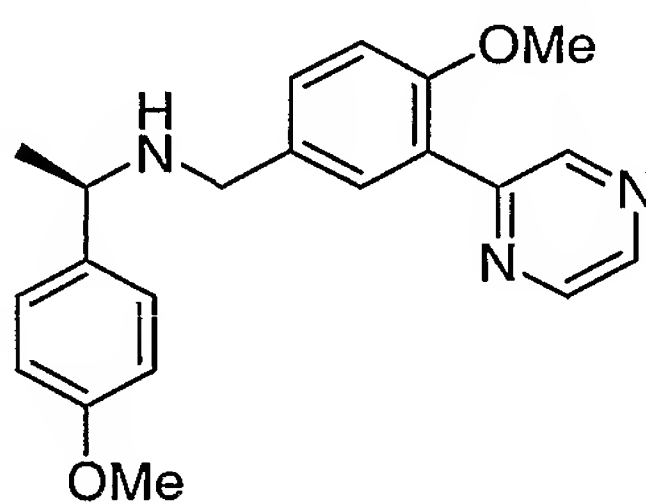


MW 349.432

Mass found: 350, 699

**Example 235**

(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)ethanamine

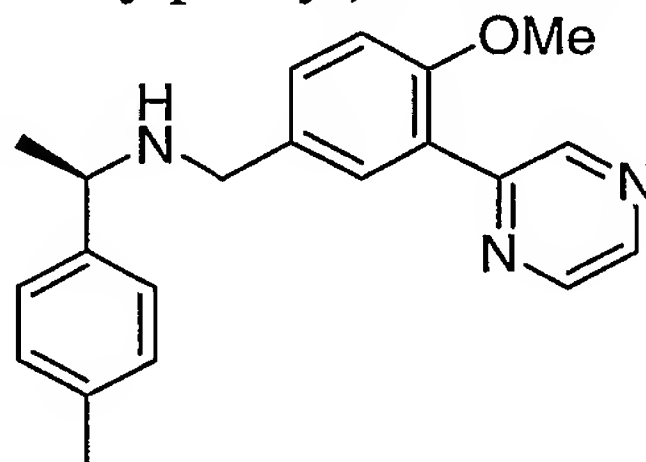


MW 349.432

Mass found: 350, 699

**Example 236**

(1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



MW 333.433

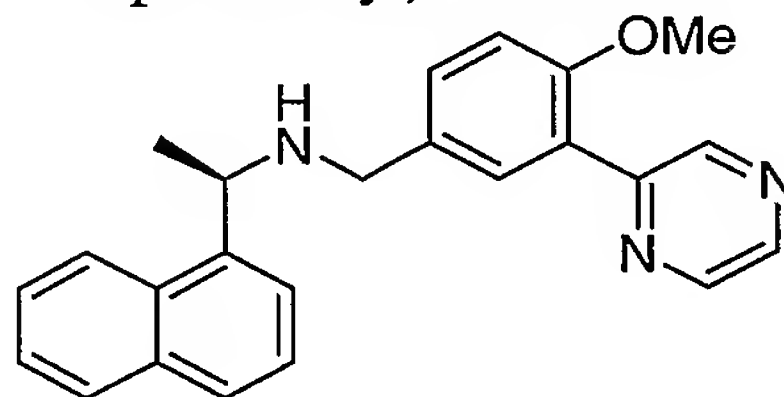
- 172 -

Mass found: 334, 667

**Example 237**

5

(1R)-N-((4-(methoxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



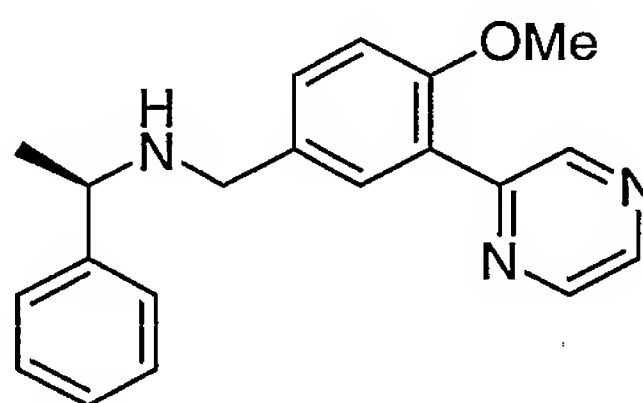
10

MW 369.466  
Mass found: 370, 739

**Example 238**

15

(1R)-N-((4-(methoxy)-3-(2-pyrazinyl)phenyl)methyl)-1-phenylethanamine



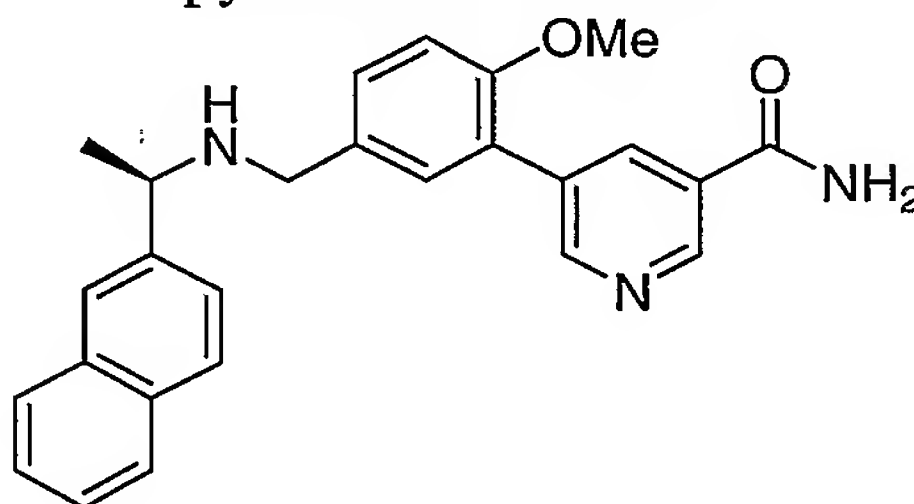
20

MW 319.406  
Mass found: 320, 639

**Example 239**

25

5-(2-(methoxy)-5-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



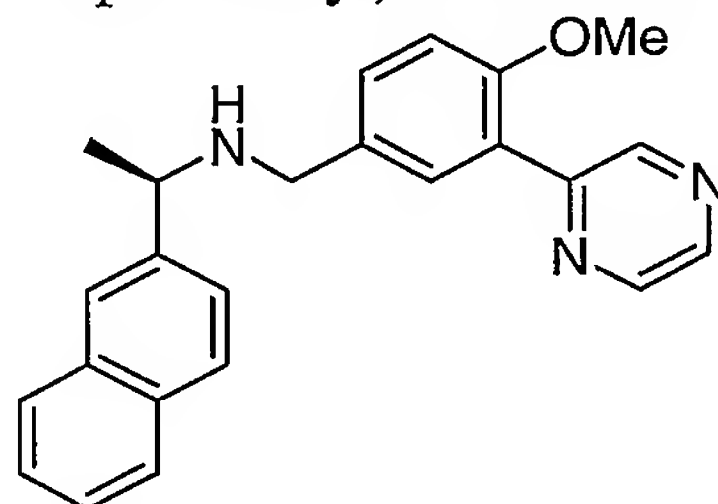
30

MW 411.503  
Mass found: 412, 453, 823, 937

- 173 -

**Example 240**

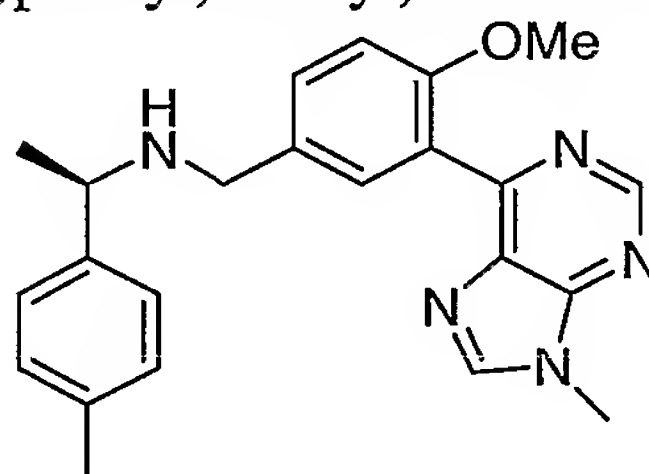
(1R)-N-((4-(methoxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine



MW 369.466  
Mass found: 370, 739

**Example 241**

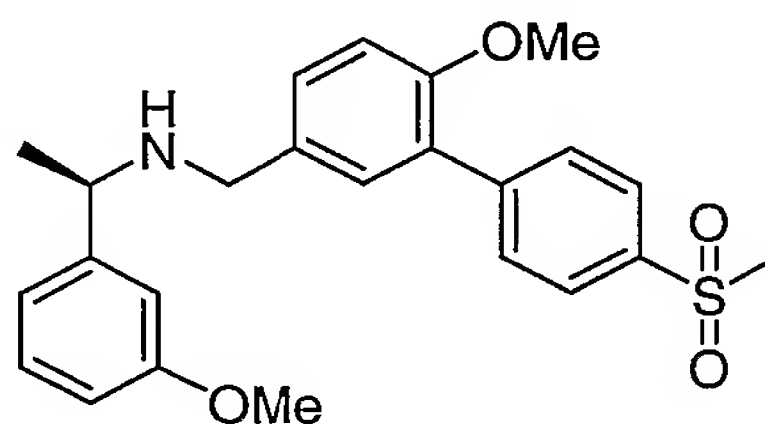
(1R)-1-(4-methylphenyl)-N-((3-(9-methyl-9H-purin-6-yl)phenyl)methyl)ethanamine



MW 357.459  
Mass found: 358, 715

**Example 242**

(1R)-N-(((6-(methoxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methoxy)phenyl)ethanamine



MW 425.546

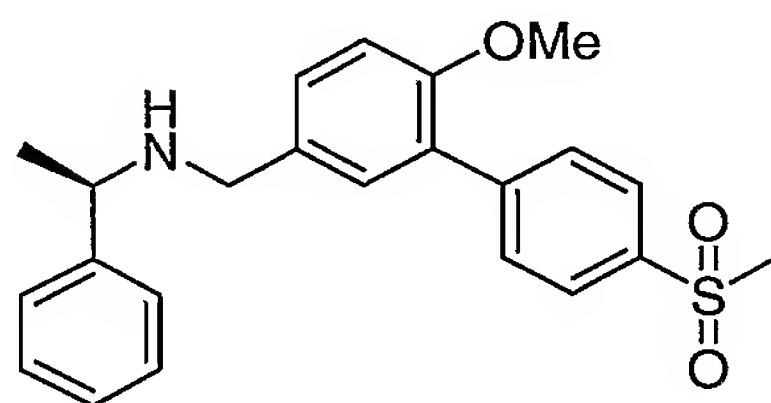
- 174 -

Mass found: 426, 851

**Example 243**

5

(1R)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



10

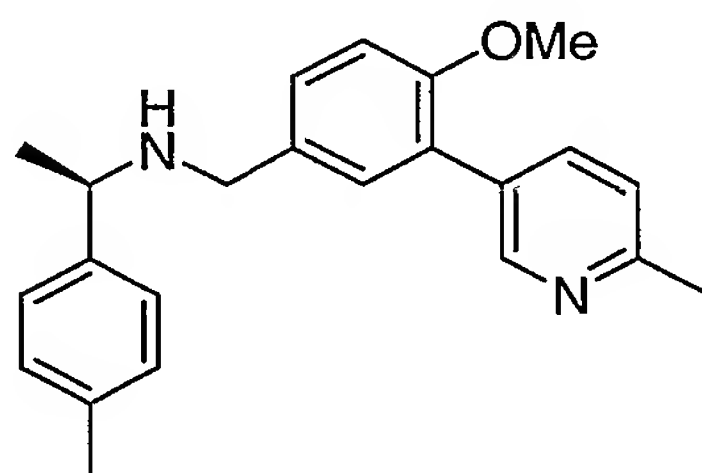
MW 395.521

Mass found: 396, 437

15

**Example 244**

(1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



20

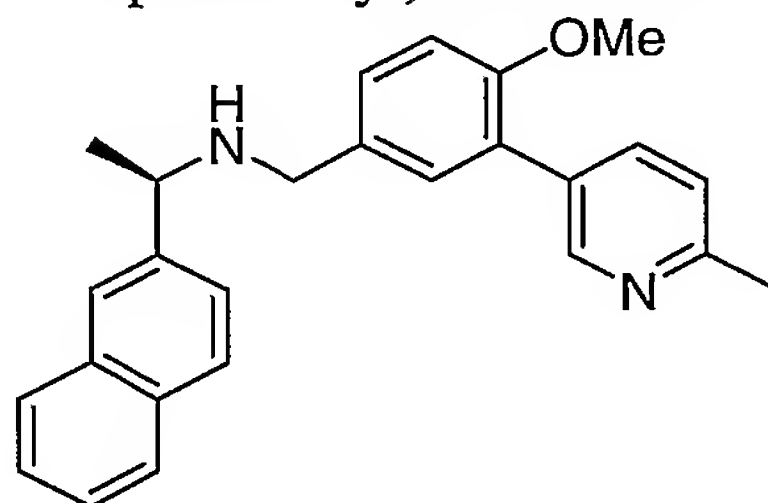
MW 346.471

Mass found: 347, 807, 693

25

**Example 245**

(1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine



30

- 175 -

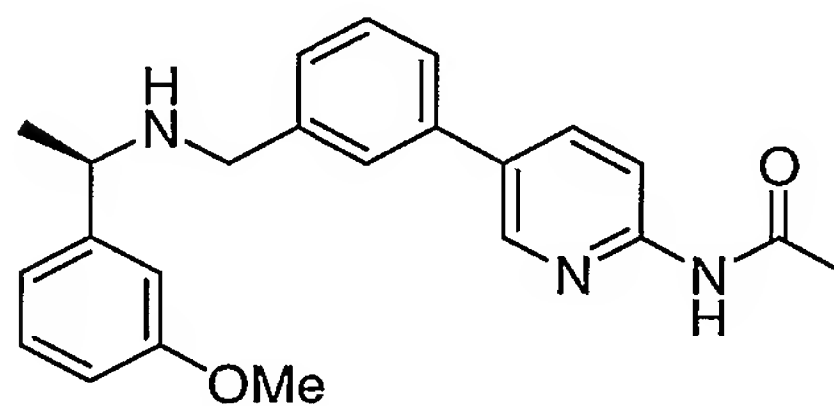
MW 382.504  
Mass found: 383, 879, 765

5

**Example 246**

N-(5-(3-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide

10



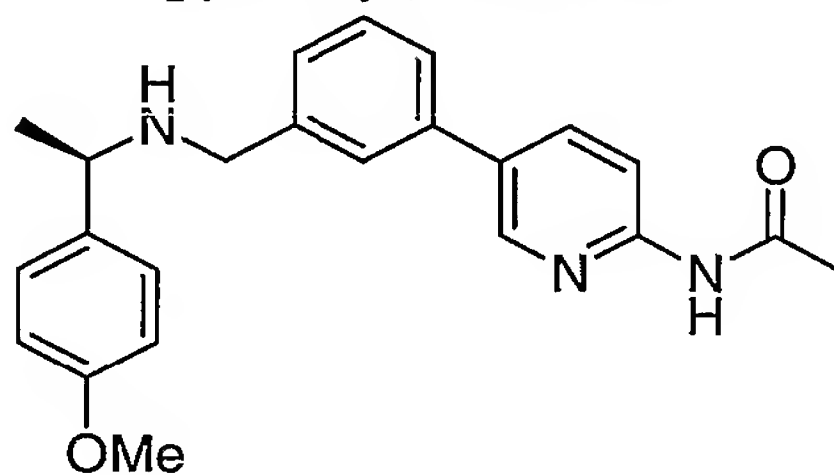
MW 375.47  
Mass found: 242, 376

15

**Example 247**

N-(5-(3-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide

20



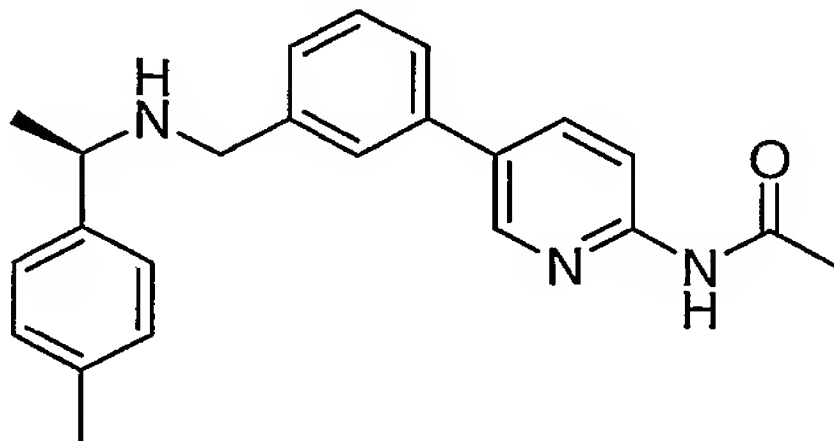
MW 375.47  
Mass found: 375, 242, 751

25

**Example 248**

N-(5-(3-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide

30





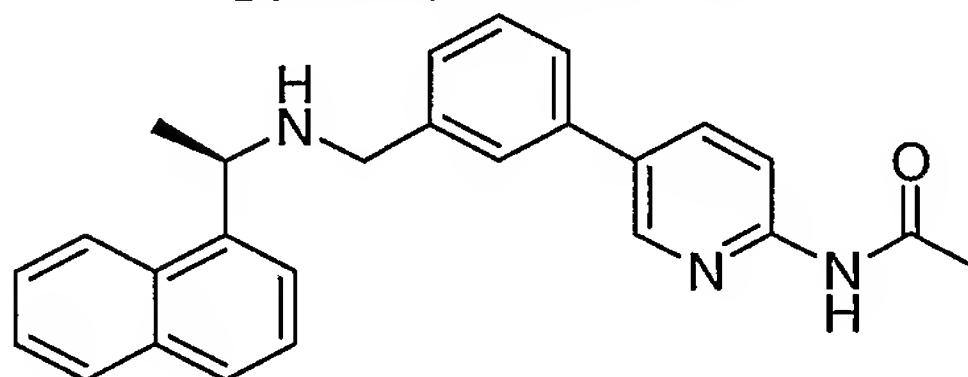
- 176 -

MW 359.47  
Mass found: 242, 360

5

**Example 249**

N-(5-(3-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide



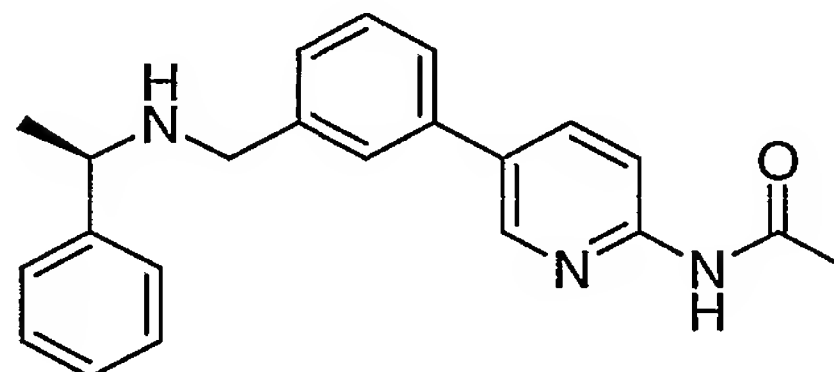
10

MW 395.504  
Mass found: 155, 242, 396

15

**Example 250**

N-(5-(3-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide



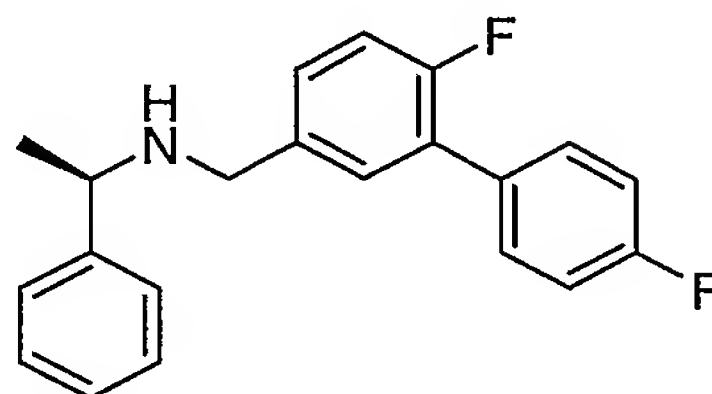
20

MW 345.444  
Mass found: 242, 346

25

**Example 251**

(1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



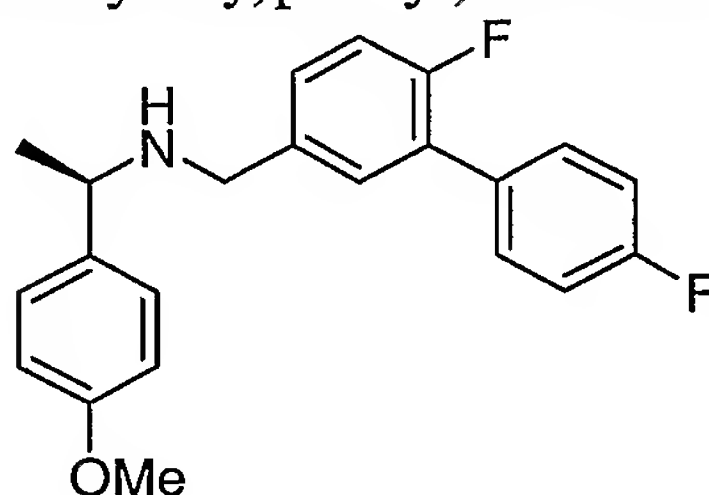
30

MW 323.384  
Mass found: 324, 647, 761

- 177 -

**Example 252**

5 (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

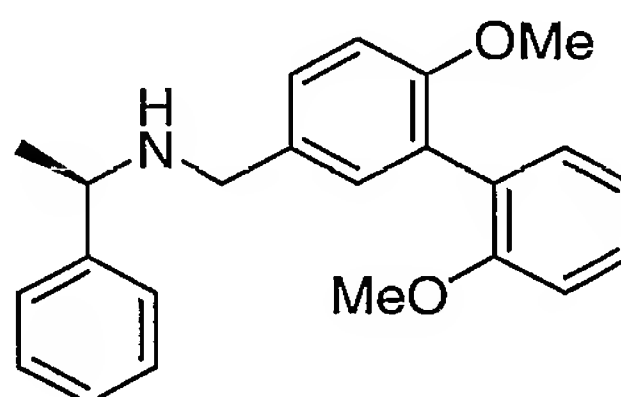


10 MW 353.41  
Mass found: 354, 707, 821

Examples 253-451 were prepared using Method C:

15 **Example 253**

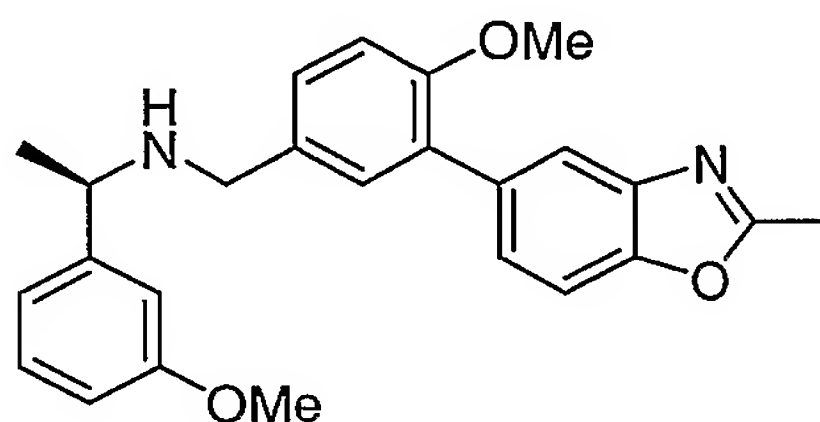
(1R)-N-((2',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



20 MW 347.456  
Mass found: 227, 348

**Example 254**

25 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

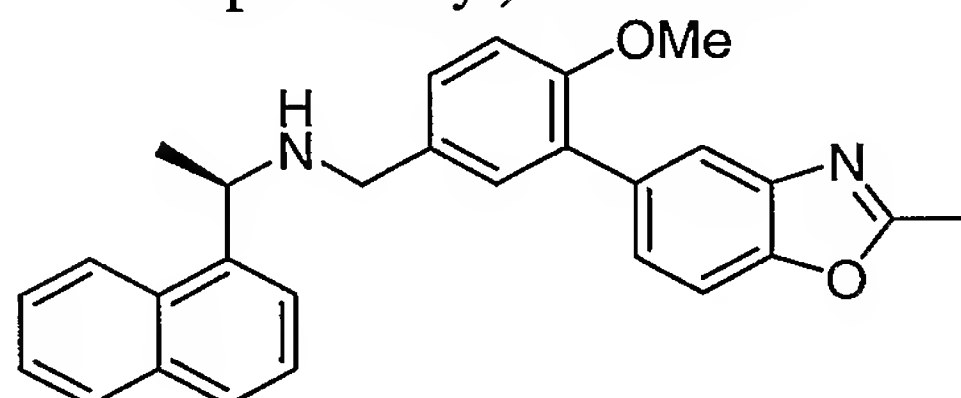


30 MW 402.491  
Mass found: 403

- 178 -

**Example 255**

5 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



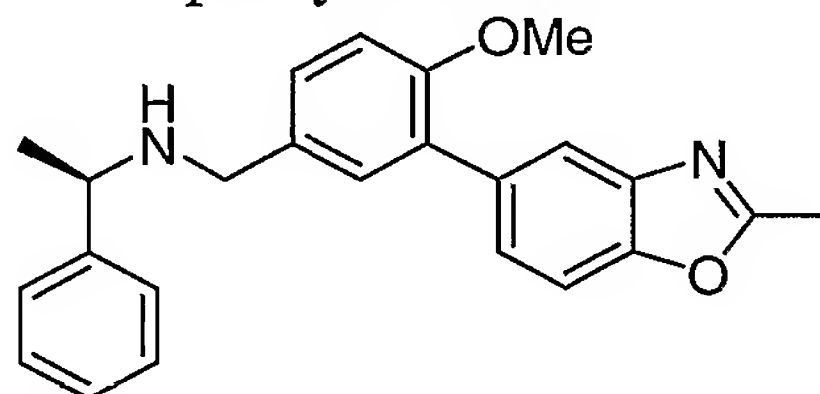
MW 422.525

Mass found: 423

10

**Example 256**

15 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



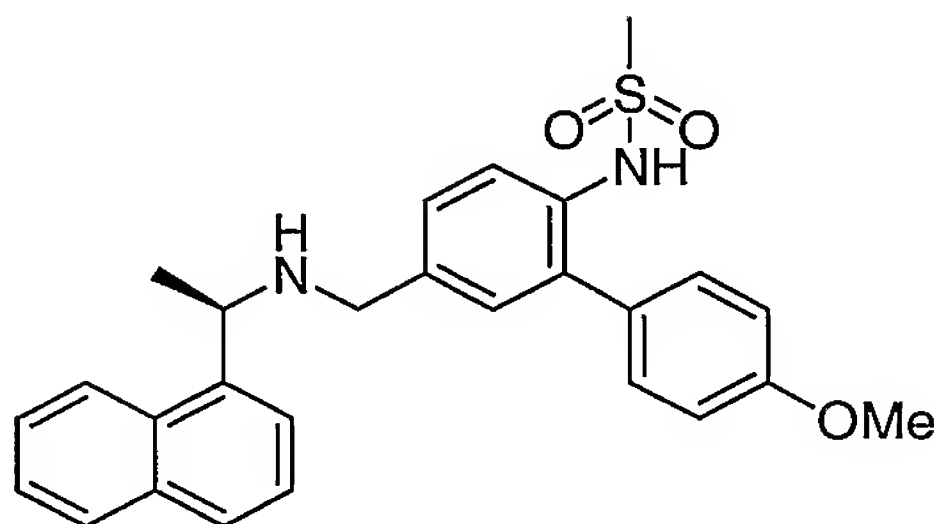
MW 372.466

Mass found: 373

20

**Example 257**

25 N-(4'-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide



MW 460.595

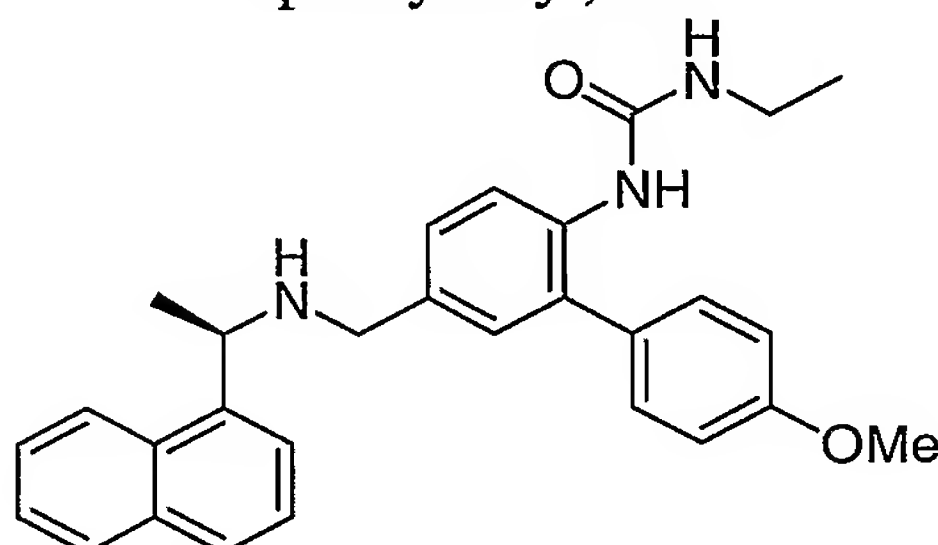
Mass found: 155, 290, 461

30

- 179 -

**Example 258**

5 N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea

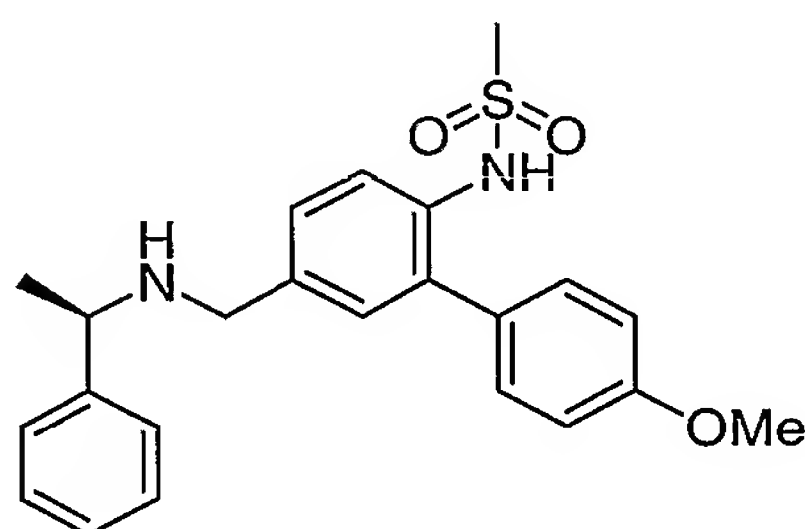


MW 453.583

Mass found: 283, 454

**Example 259**

15 N-(4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide

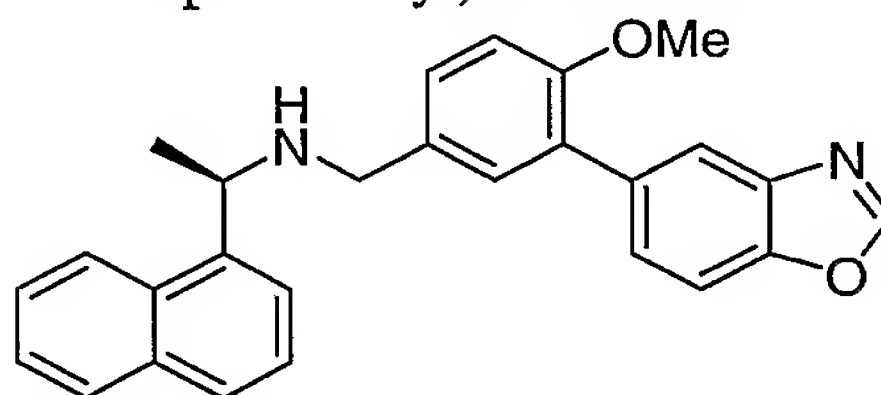


MW 410.535

Mass found: 411

**Example 260**

25 (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



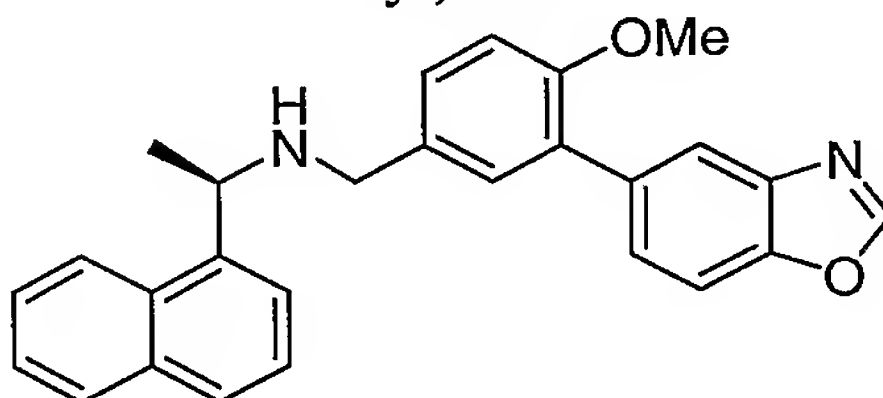
- 180 -

MW 408.499  
Mass found: 409

5

**Example 261**

N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea



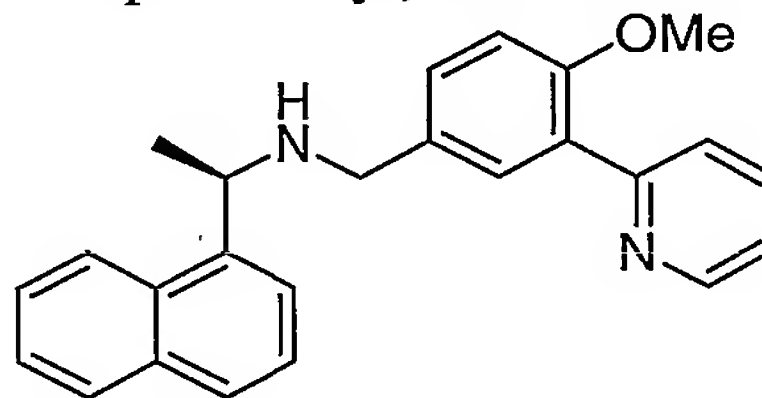
10

MW 403.523  
Mass found: 404, 283

15

**Example 262**

(1R)-N-((4-(methyloxy)-3-(2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



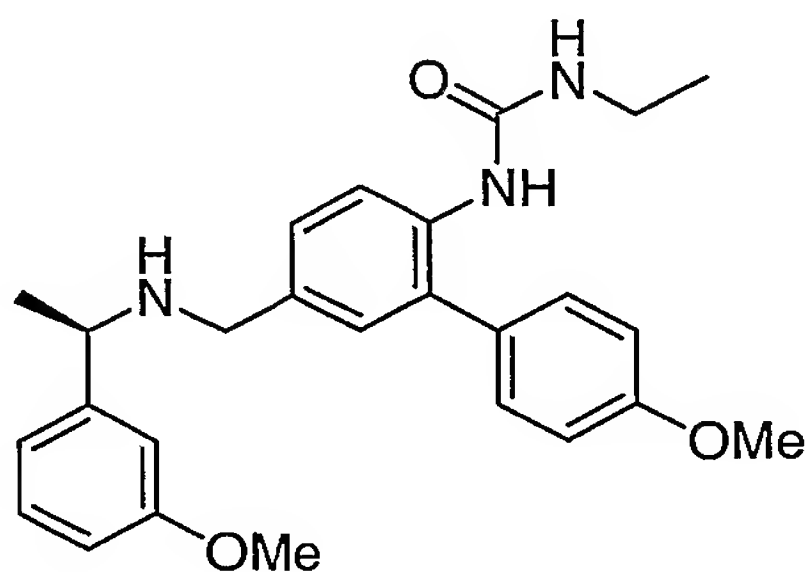
20

MW 368.478  
Mass found: 369, 737

25

**Example 263**

N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea



30

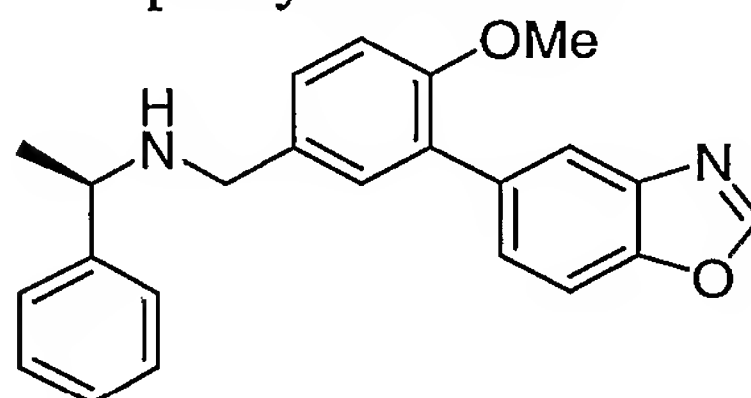
- 181 -

MW 433.549  
Mass found: 434

5

**Example 264**

(1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



10

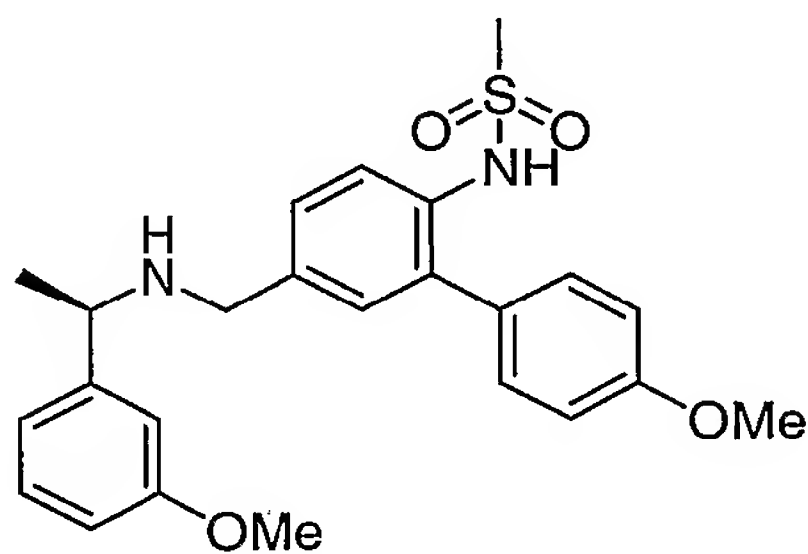
MW 358.439  
Mass found: 359

15

**Example 265**

N-(4'-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide

20



25

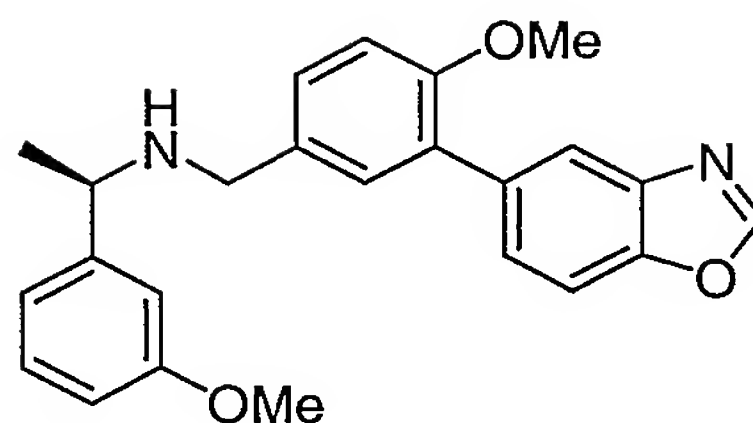
MW 440.561  
Mass found: 290, 441

**Example 266**

(1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

30

- 182 -



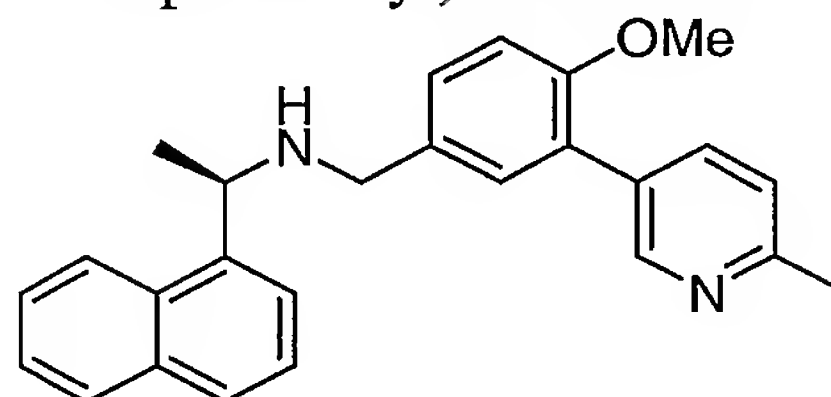
MW 388.465  
Mass found: 389, 891

5

**Example 267**

(1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

10



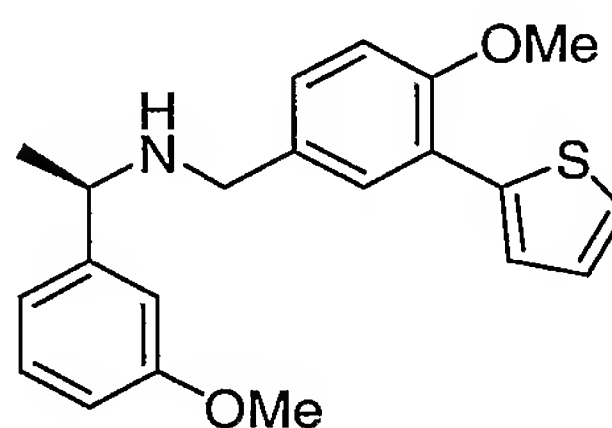
MW 382.504  
Mass found: 383, 229, 155

15

**Example 268**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)ethanamine

20



MW 353.484  
Mass found: 354

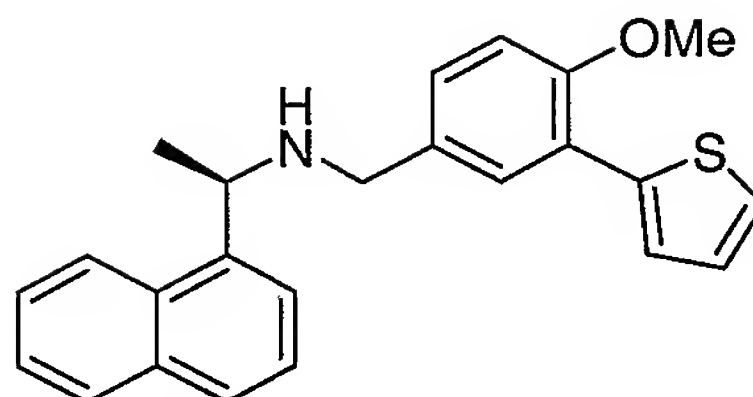
25

**Example 269**

(1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 183 -



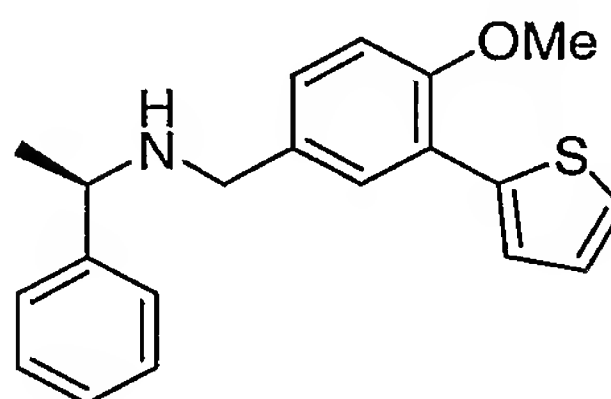
MW 373.518  
Mass found: 374

5

**Example 270**

(1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-phenylethanamine

10



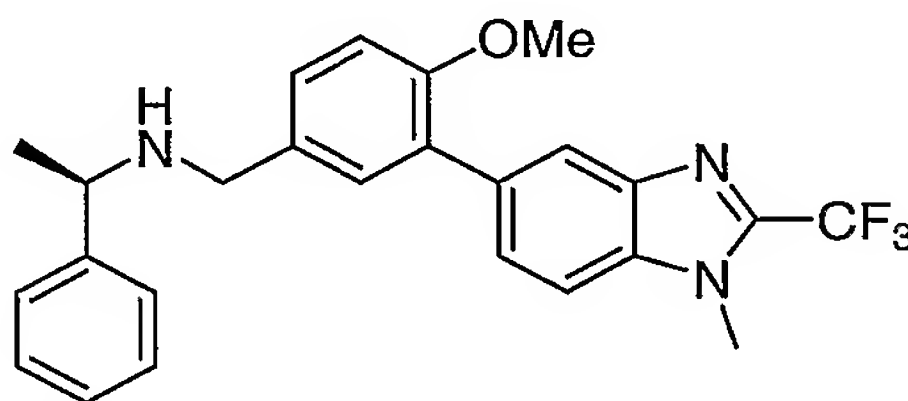
MW 323.458  
Mass found: 324, 203, 647

15

**Example 271**

(1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-phenylethanamine

20



MW 439.479  
Mass found: 440, 481

25

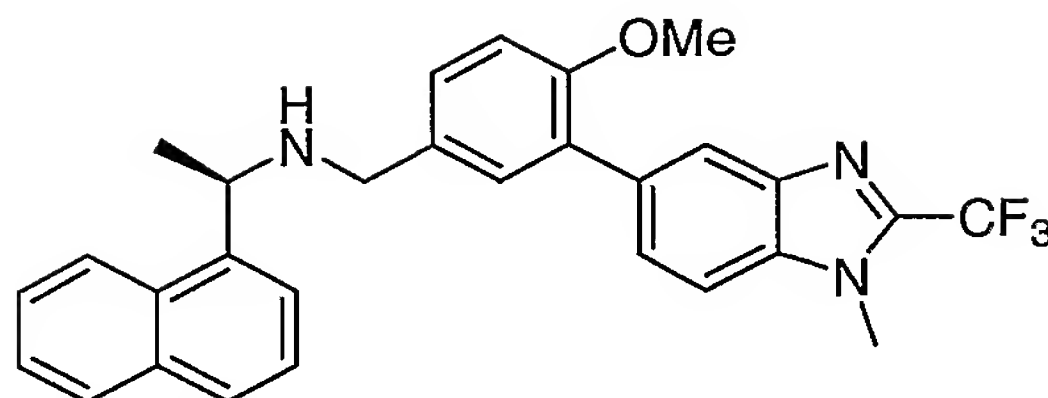
**Example 272**

(1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30



- 184 -

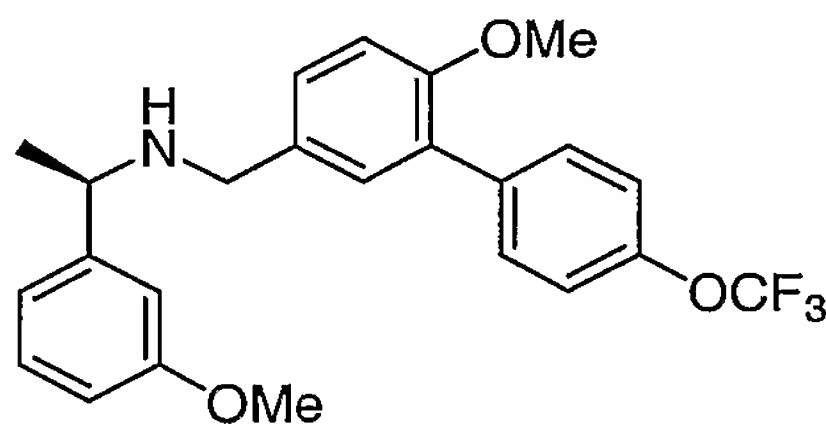


MW 489  
Mass found: 490, 155

5

**Example 273**

10 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine

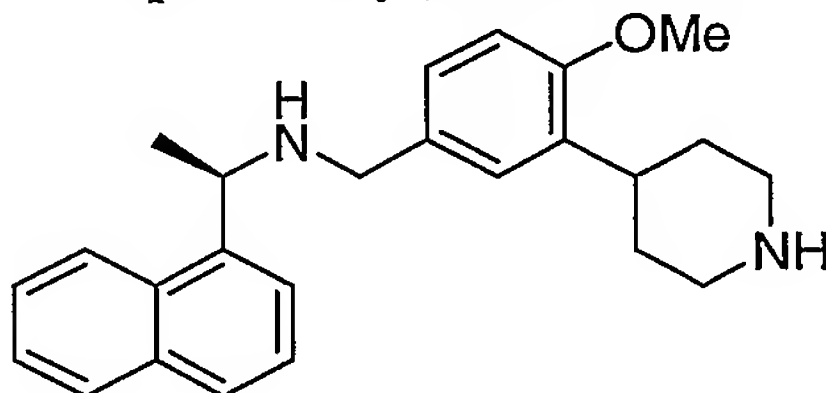


MW 431.452  
Mass found: 432

15

**Example 274**

20 (1R)-N-((4-(methyloxy)-3-(4-piperidiny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



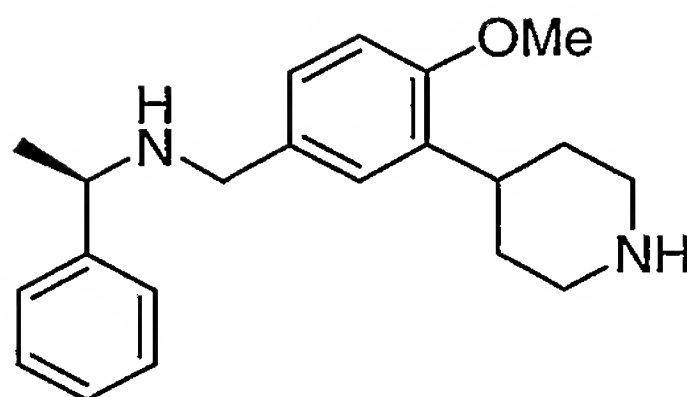
MW 374.525  
Mass found: 375, 489, 155

25

**Example 275**

30 (1R)-N-((4-(methyloxy)-3-(4-piperidiny)phenyl)methyl)-1-phenylethanamine

- 185 -



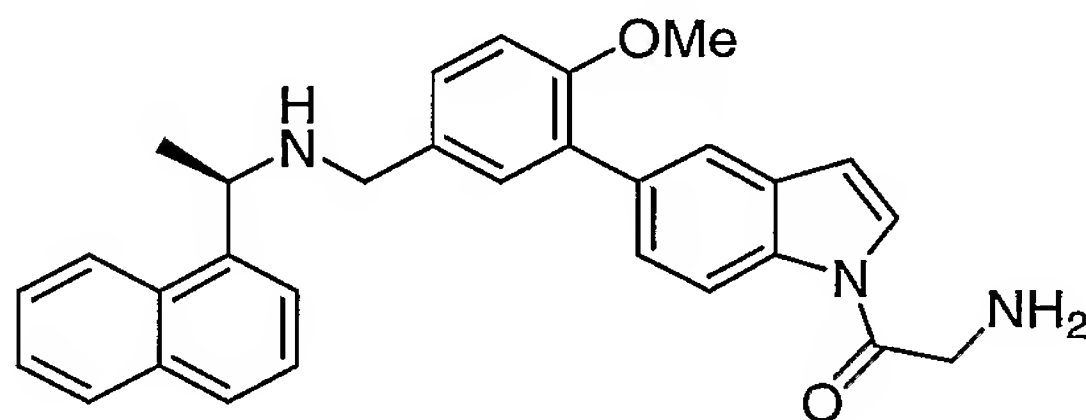
MW 324.465  
Mass found: 325, 439

5

**Example 276**

2-(5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide

10



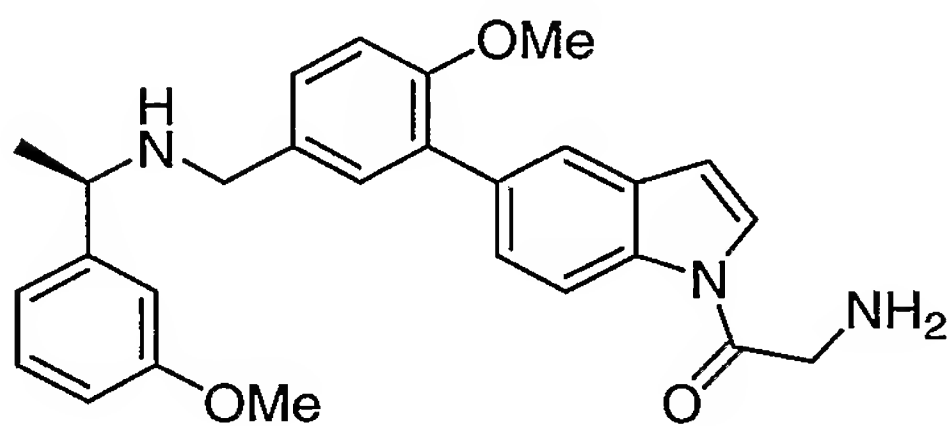
MW 463.578  
Mass found: 464

15

**Example 277**

2-(5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide

20



MW 443.544  
Mass found: 444

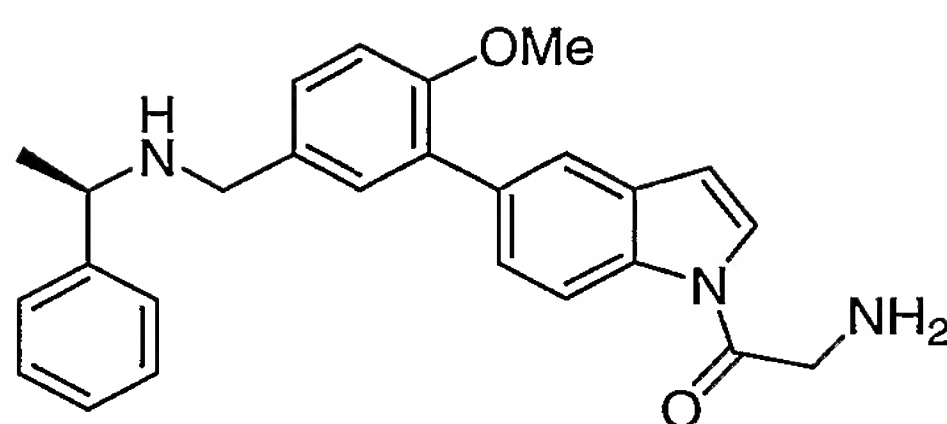
25

**Example 278**

2-(5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide

30

- 186 -

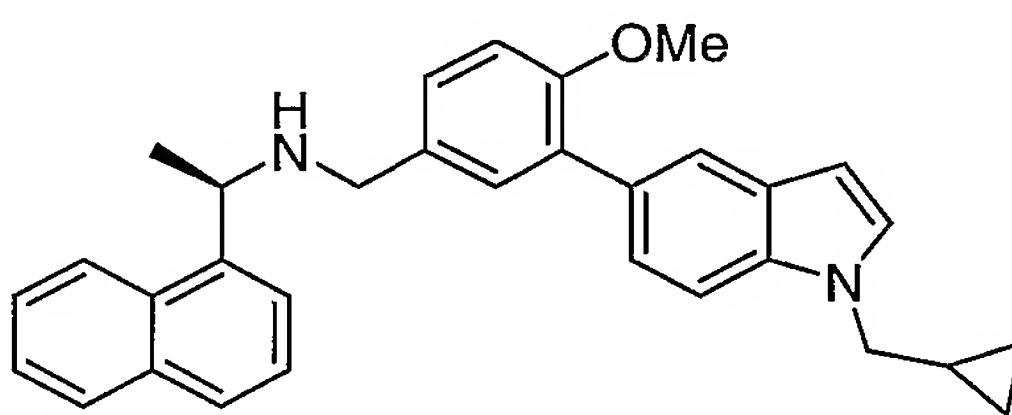


MW 413.518  
Mass found: 414

5

**Example 279**

10 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-  
1-(1-naphthalenyl)ethanamine

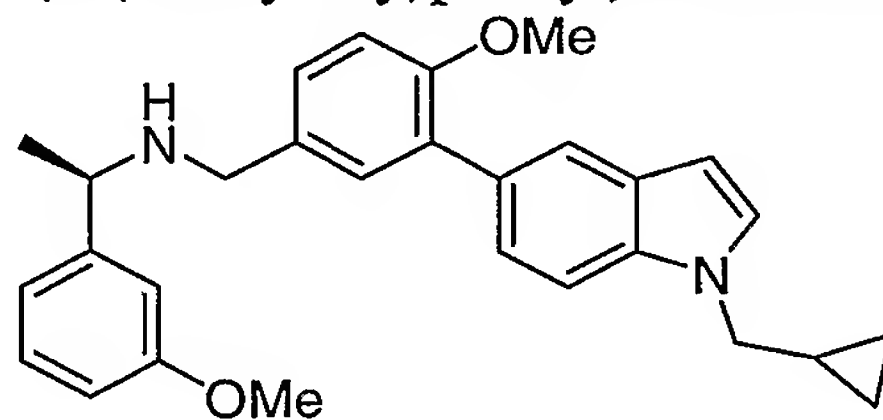


MW 460.618  
Mass found: 491

15

**Example 280**

20 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-  
1-(3-(methyloxy)phenyl)ethanamine



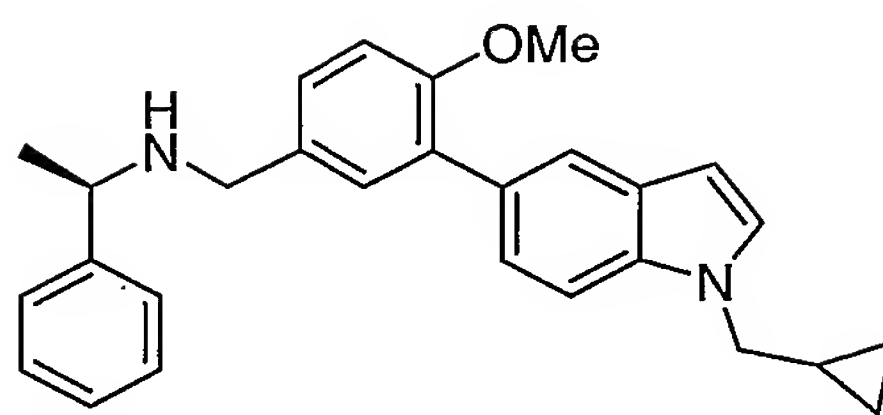
MW 440.584  
Mass found: 441

25

**Example 281**

30 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-  
1-phenylethanamine

- 187 -

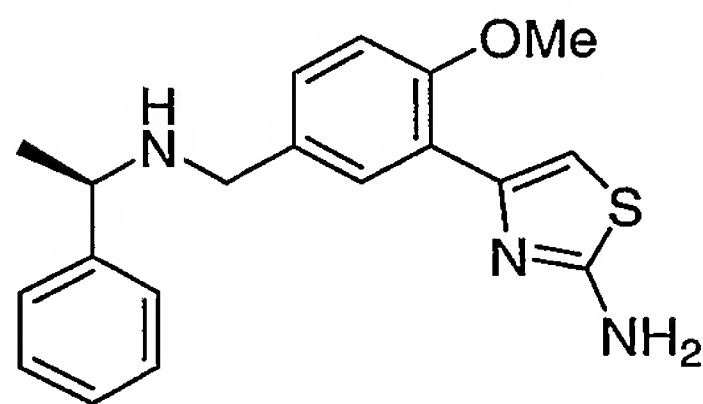


MW 410.558  
Mass found: 411

- 188 -

**Example 282**

4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1,3-thiazol-2-amine

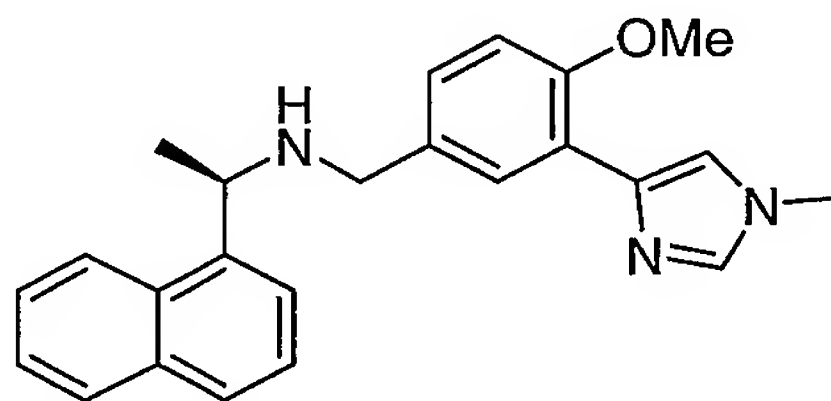


MW 339.461

Mass found: 340, 679

**Example 283**

(1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

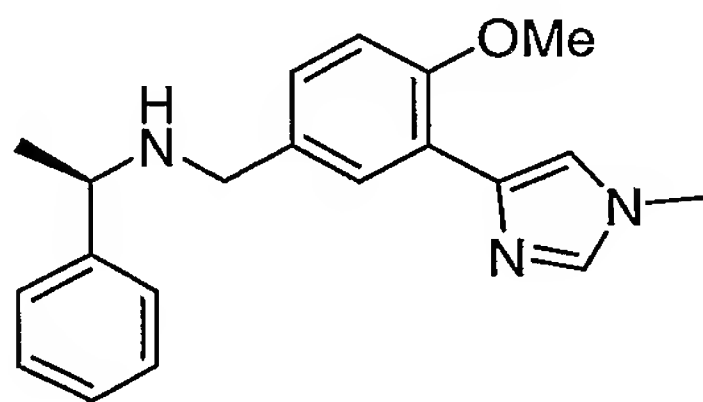


MW 371.482

Mass found: 372, 155, 743

**Example 284**

(1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



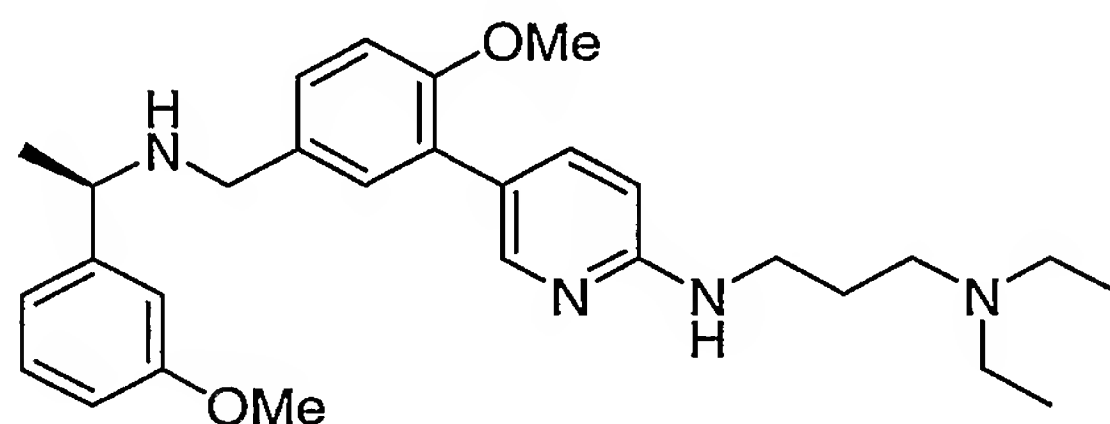
MW 321.422

Mass found: 322, 643

**Example 285**

- 189 -

N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methoxy)phenyl)methyl)-N-((1R)-1-(3-(methoxy)phenyl)ethyl)amine

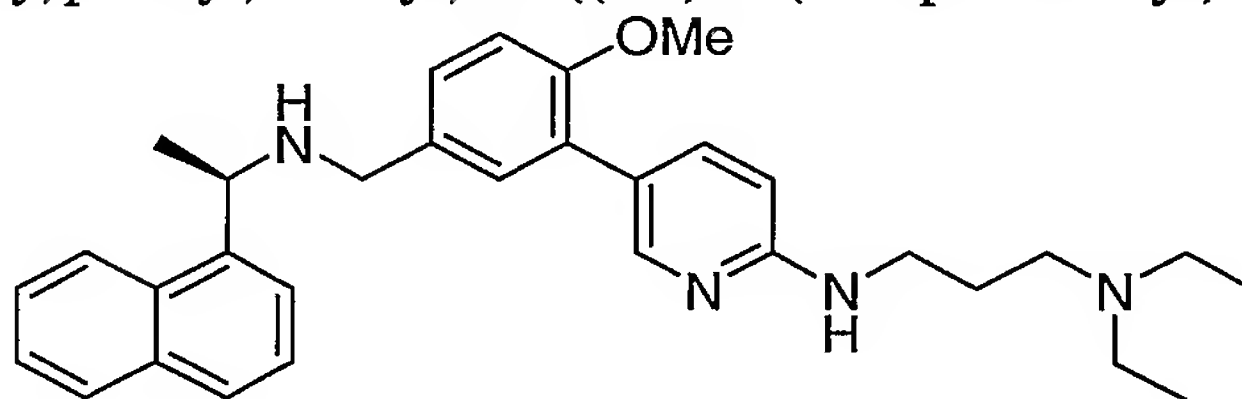


MW 477.645  
Mass found: 478, 344

10

**Example 286**

N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methoxy)phenyl)methyl)-N-((1R)-1-(1-naphthalenyl)ethyl)amine

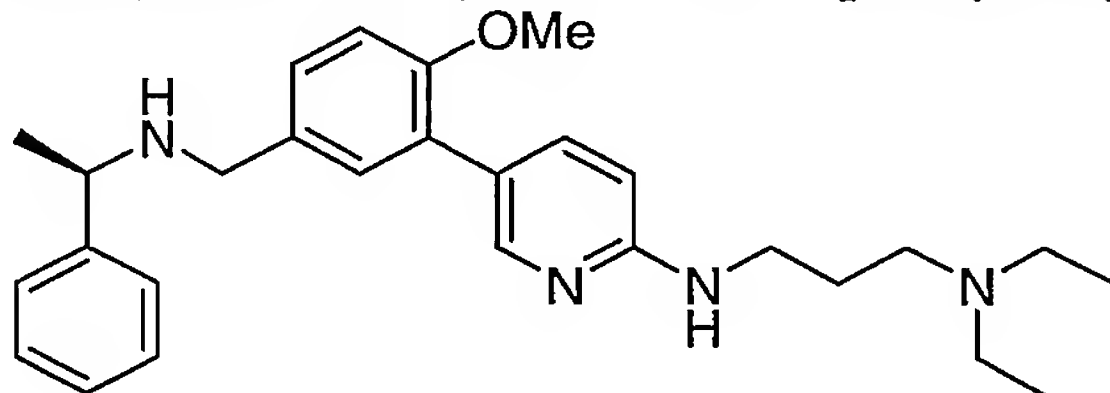


MW 497.679  
Mass found: 498, 155, 344

20

**Example 287**

N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methoxy)phenyl)methyl)-N-((1R)-1-phenylethyl)amine



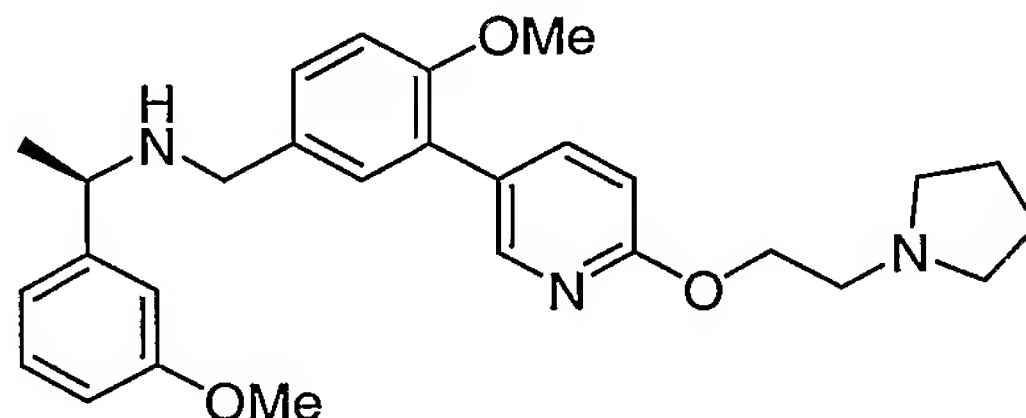
MW 447.619  
Mass found: 448, 344

30

**Example 288**

- 190 -

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine



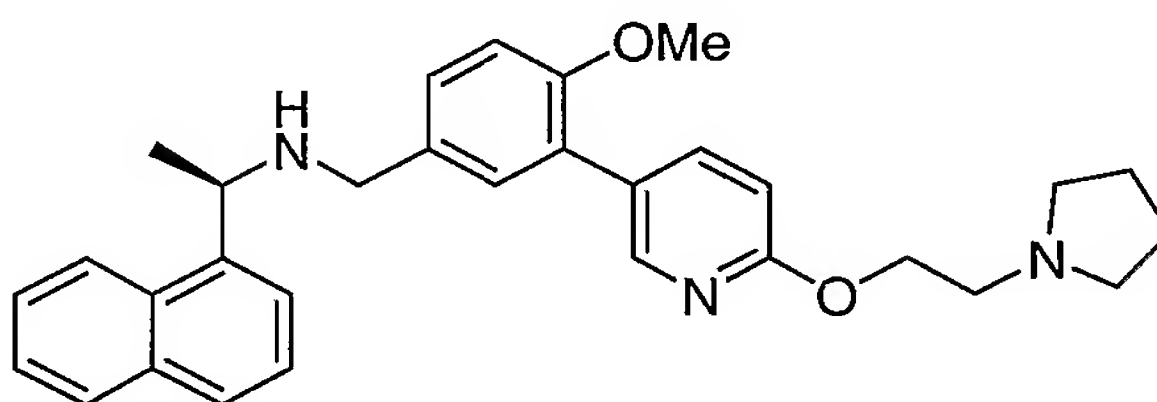
5

MW 461.603  
Mass found: 462, 328

10

**Example 289**

(1R)-N-((4-(methyloxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



15

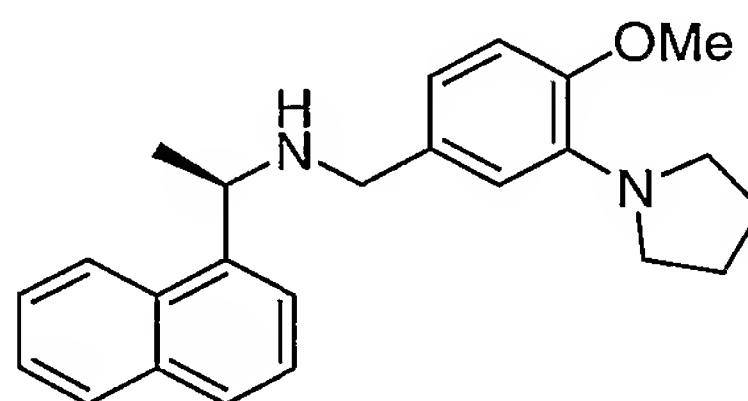
MW 481.637  
Mass found: 155, 482, 328

20

**Example 290**

(1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

25



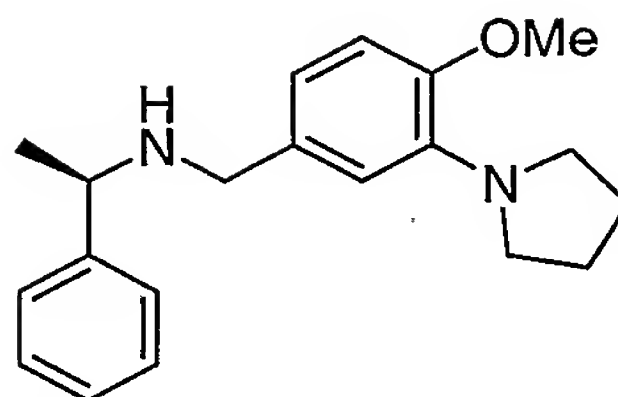
30

MW 360.498  
Mass found: 361, 721

**Example 291**

(1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-phenylethanamine

- 191 -



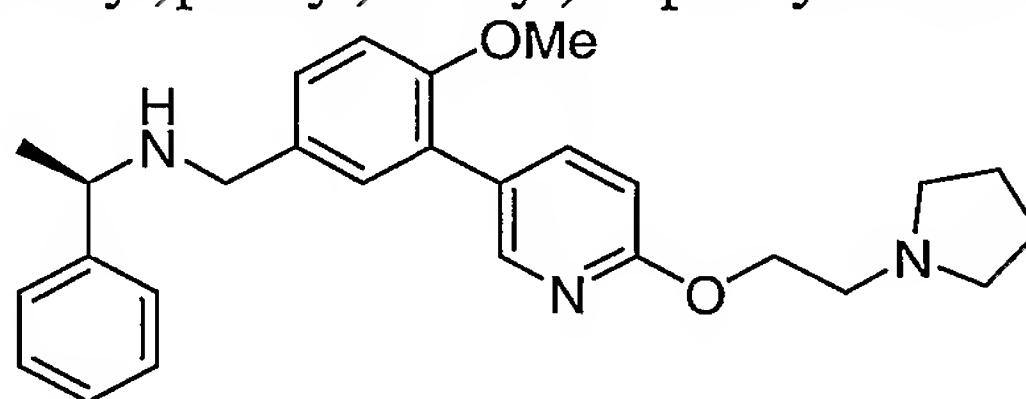
MW 310.438  
Mass found: 311, 621

5

**Example 292**

(1R)-N-((4-(methyloxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

10



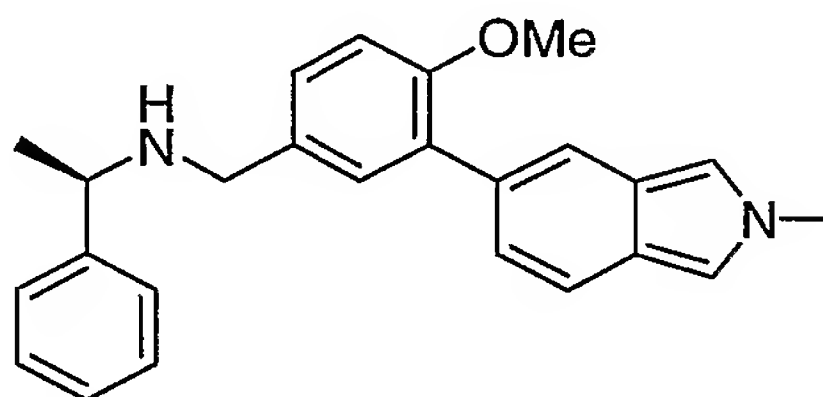
MW 431.577  
Mass found: 432, 328

15

**Example 293**

(1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

20



MW 371.482  
Mass found: 372, 744, 858

25

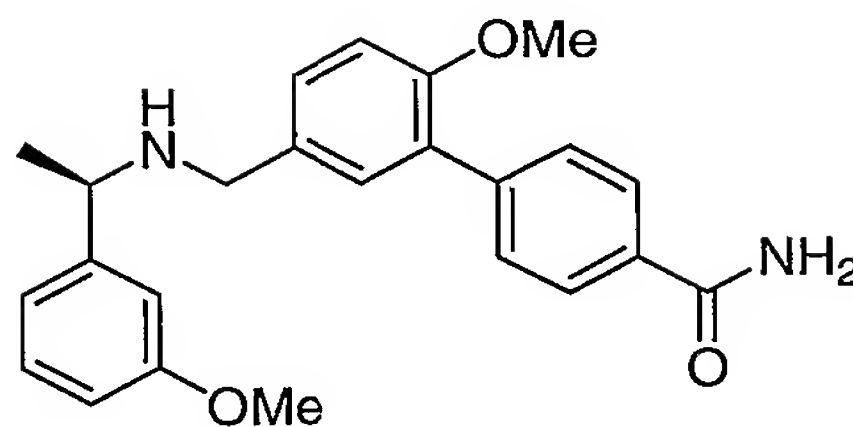
**Example 294**

2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide

30



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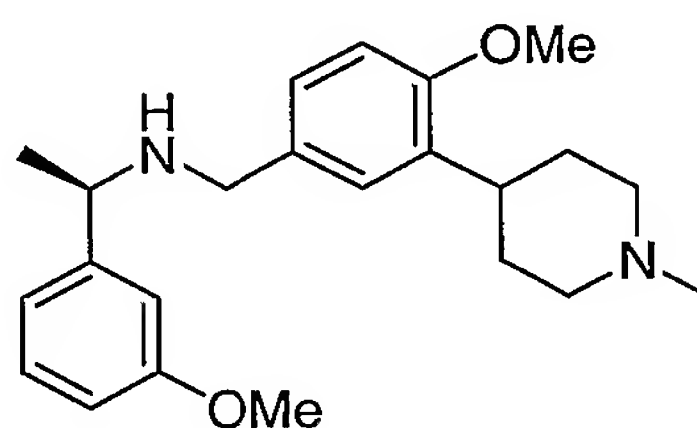
MW 390.48  
Mass found: 240, 391, 781

5

**Example 295**

(1R)-N-((4-(methyloxy)-3-(1-methyl-4-piperidiny)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



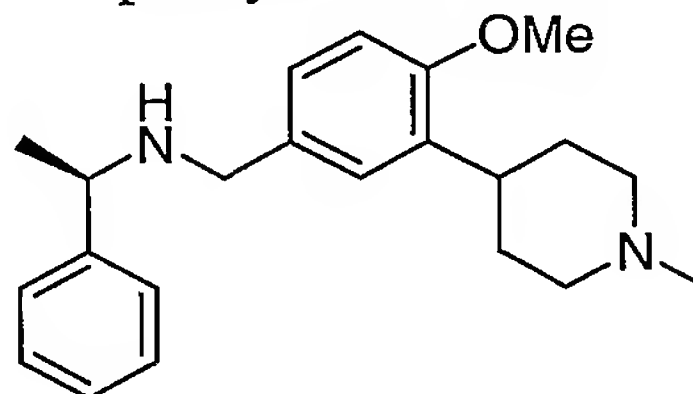
MW 368.518  
Mass found: 369, 483

15

**Example 296**

(1R)-N-((4-(methyloxy)-3-(1-methyl-4-piperidiny)phenyl)methyl)-1-phenylethanamine

20



MW 338.492  
Mass found: 339, 453

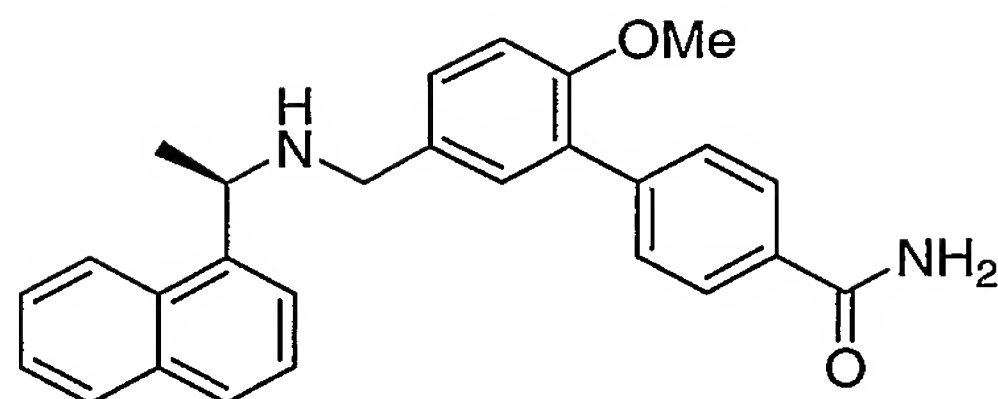
25

**Example 297**

2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide

30

- 193 -



MW 410.514

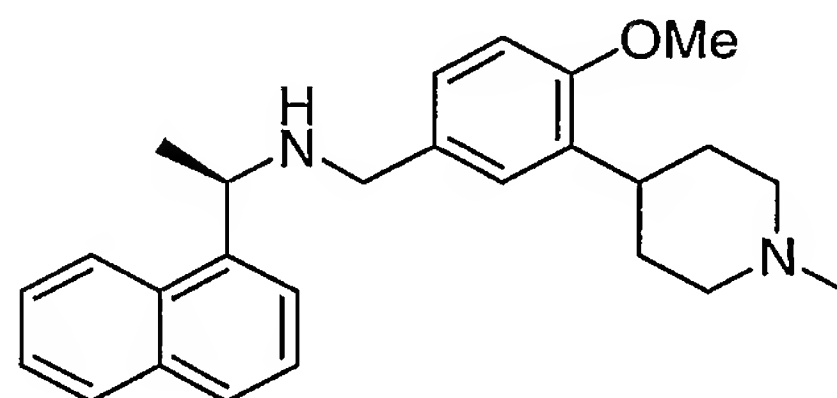
Mass found: 155, 411, 240, 257

5

**Example 298**

(1R)-N-((4-(methyloxy)-3-(1-methyl-4-piperidiny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

10



MW 388.552

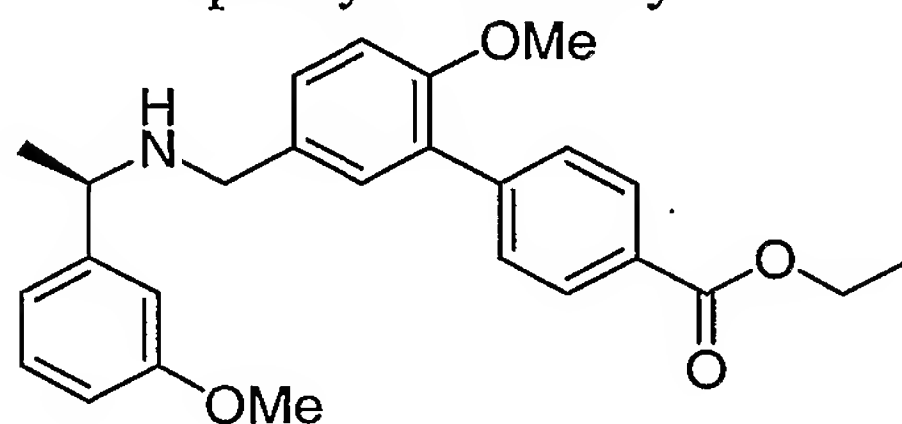
Mass found: 389, 503

15

**Example 299**

ethyl 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate

20



MW 419.518

Mass found: 953, 420

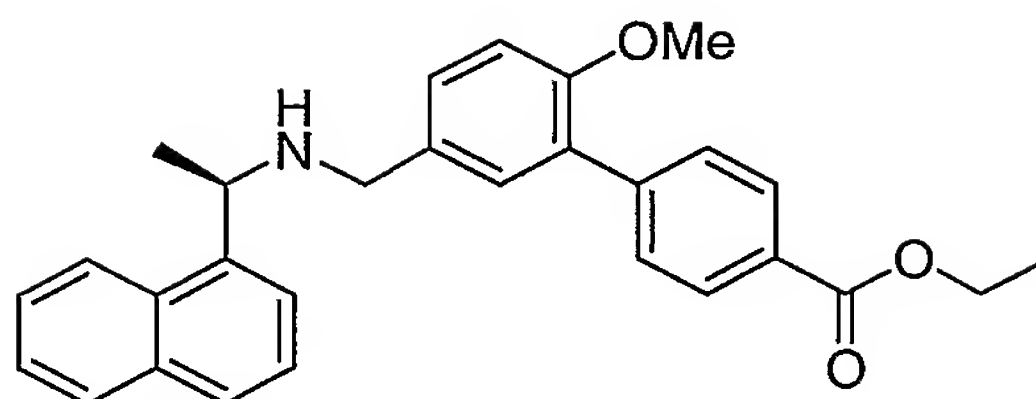
25

**Example 300**

ethyl 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate

30

- 194 -



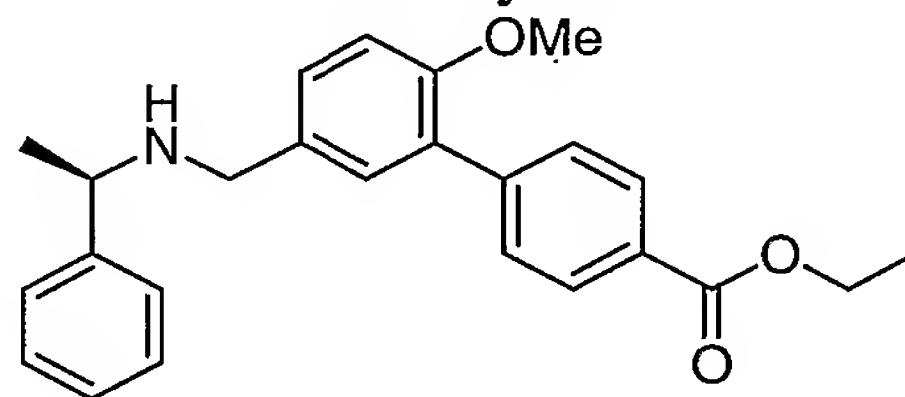
MW 439.552  
Mass found: 440, 993

5

**Example 301**

ethyl 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-  
carboxylate

10



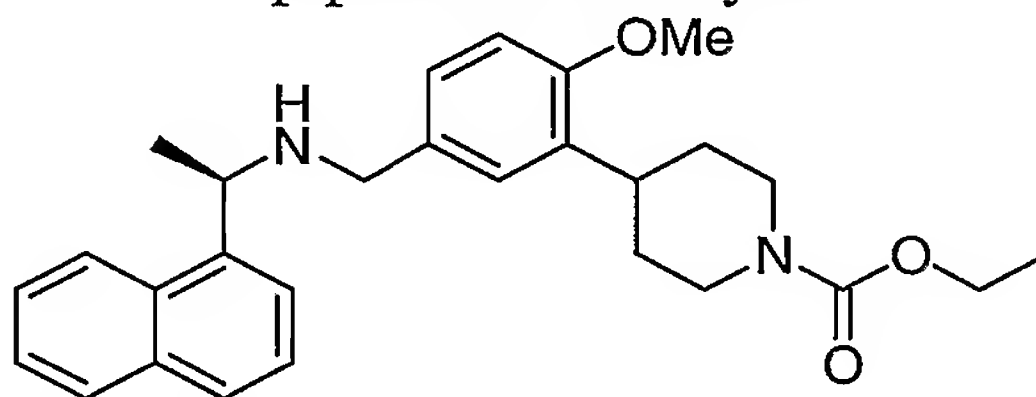
MW 389.492  
Mass found: 390, 893

15

**Example 302**

ethyl 4-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-  
1-piperidinecarboxylate

20



MW 446.588  
Mass found: 447

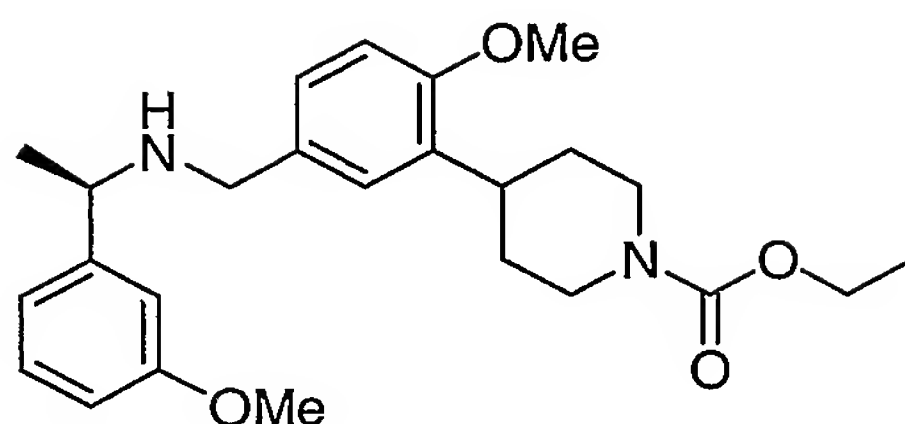
25

**Example 303**

ethyl 4-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-1-piperidinecarboxylate

30

- 195 -



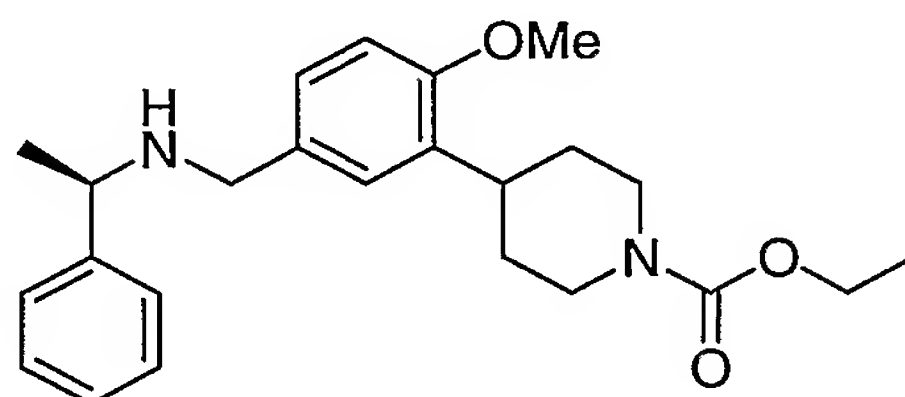
MW 426.554  
Mass found: 427, 967

5

**Example 304**

ethyl 4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1-piperidinecarboxylate

10



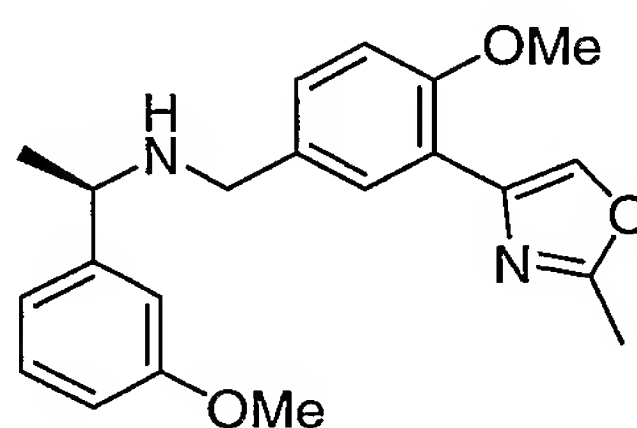
MW 396.528  
Mass found: 397, 907

15

**Example 305**

(1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

20



MW 352.432  
Mass found: 353, 705

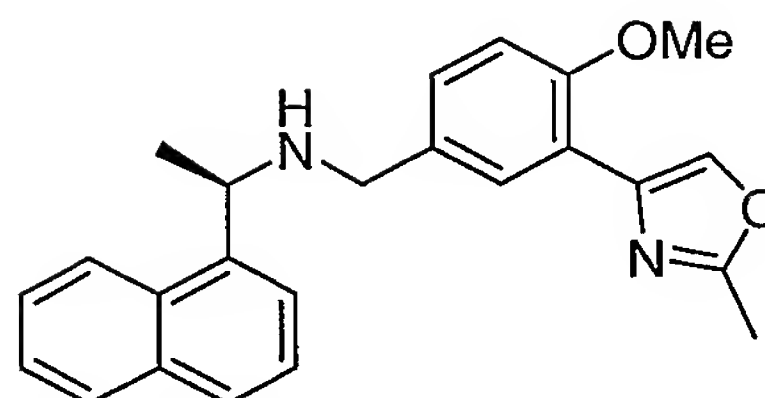
25

**Example 306**

(1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 196 -



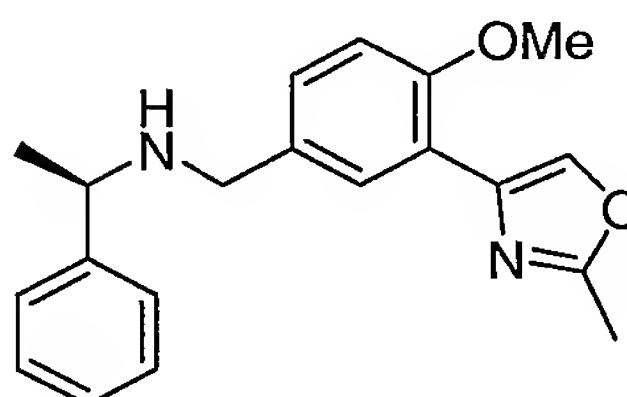
MW 372.466  
Mass found: 373, 745

5

**Example 307**

(1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

10



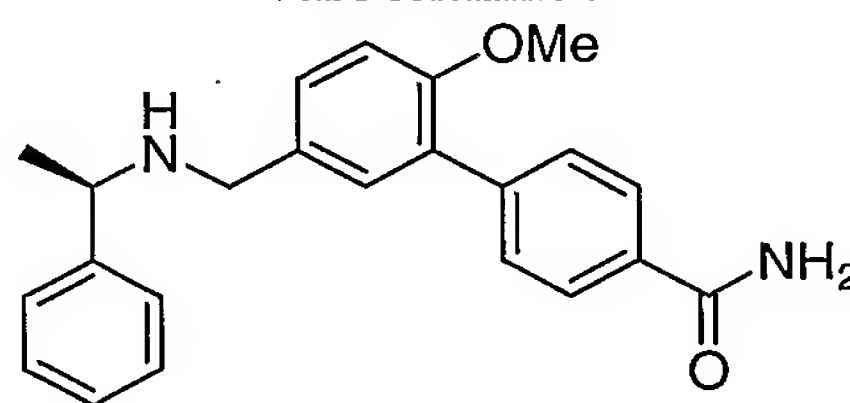
MW 322.406  
Mass found: 323, 645

15

**Example 308**

2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide

20



MW 360.455  
Mass found: 835, 361

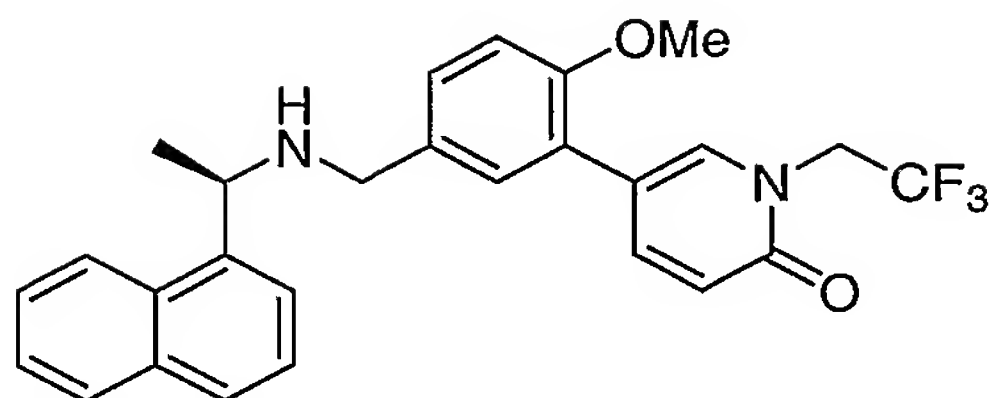
25

**Example 309**

5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-1-(2,2,2-trifluoroethyl)-2(1H)-pyridinone

30

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MW 466.5

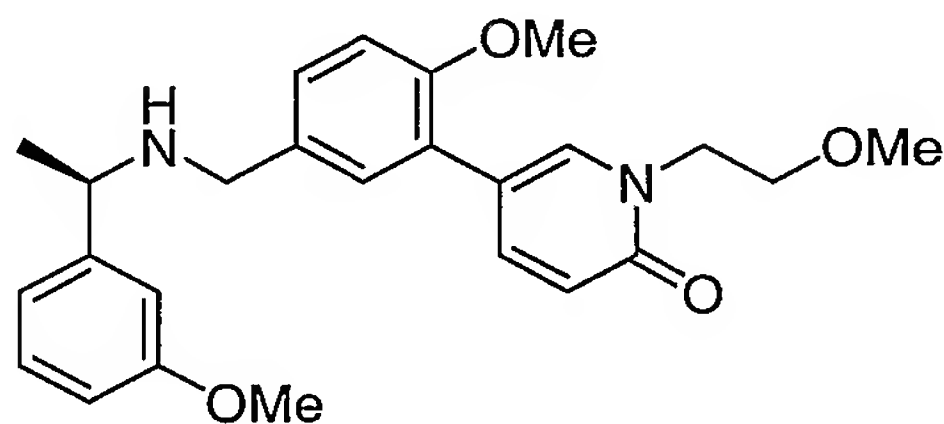
Mass found: 155, 296, 467

5

**Example 310**

1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-(((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone

10



MW 422.522

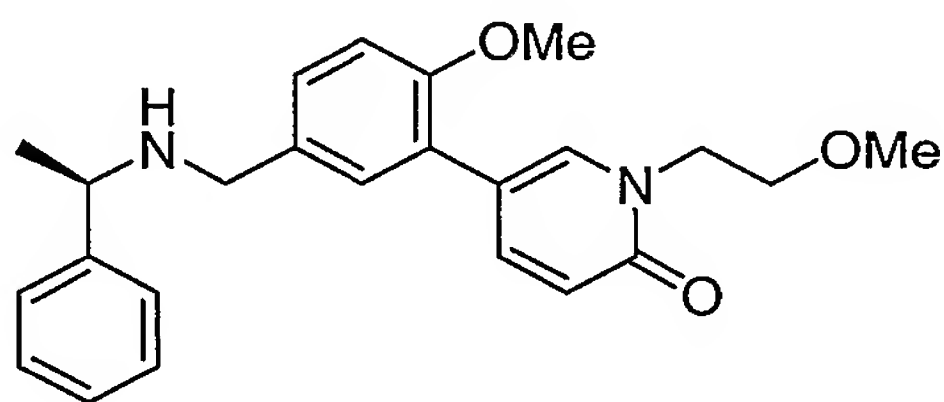
Mass found: 272, 423, 290

15

**Example 311**

1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-(((1R)-1-phenylethyl)amino)methyl)phenyl)-2(1H)-pyridinone

20



MW 392.496

Mass found: 272, 393

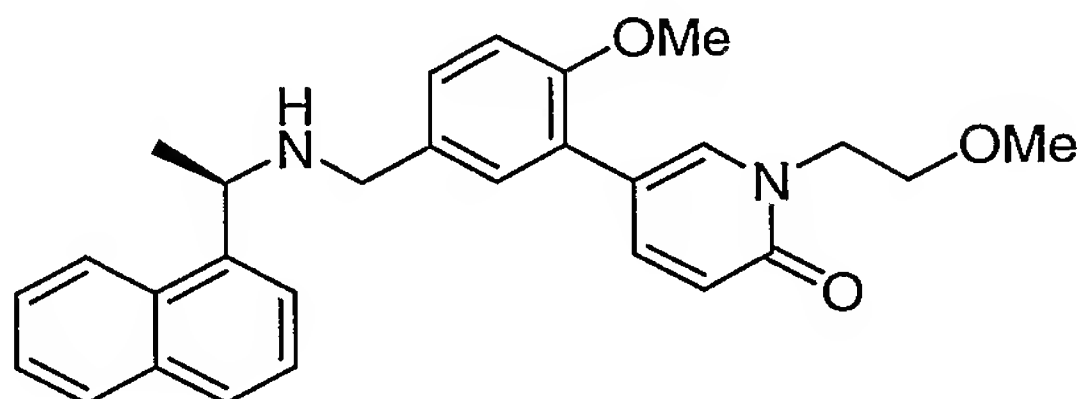
25

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**Example 312**

1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-(((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone

5



MW 442.556

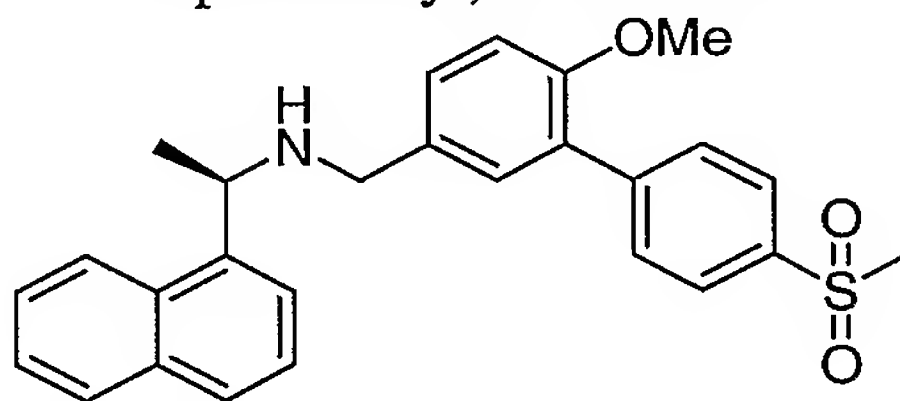
Mass found: 289, 272, 443

10

**Example 313**

(1R)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 445.58

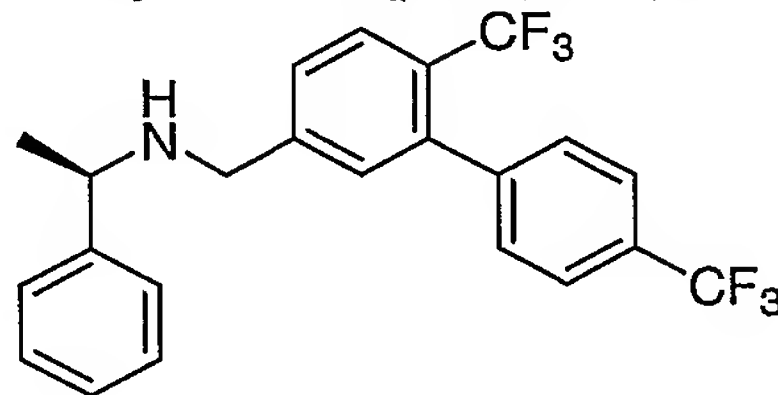
Mass found: 155, 446, 275

20

**Example 314**

(1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

25



MW 423.398

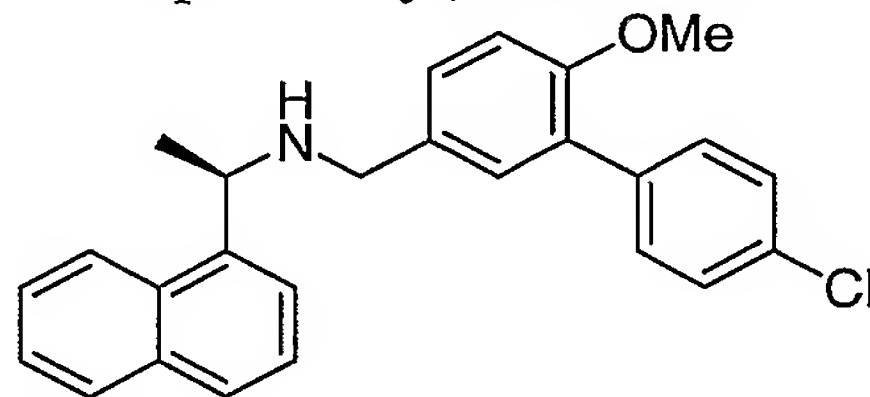
Mass found: 424, 361

30

**Example 315**

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(1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



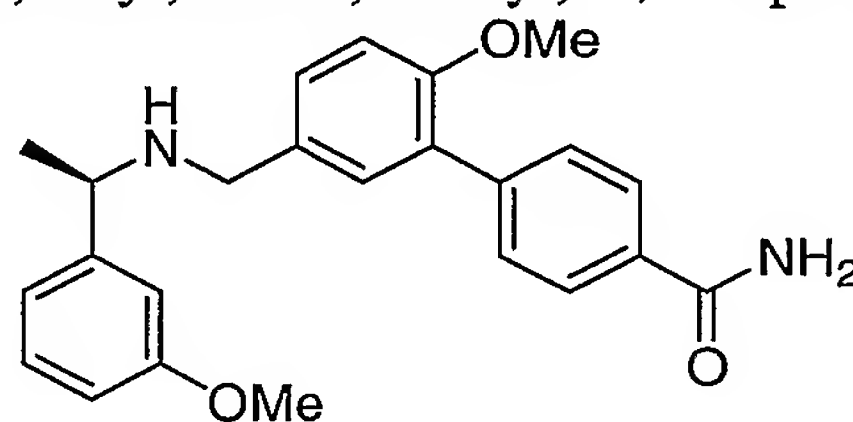
5

MW 401.935  
Mass found: 155, 231, 402

**Example 316**

10

N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide



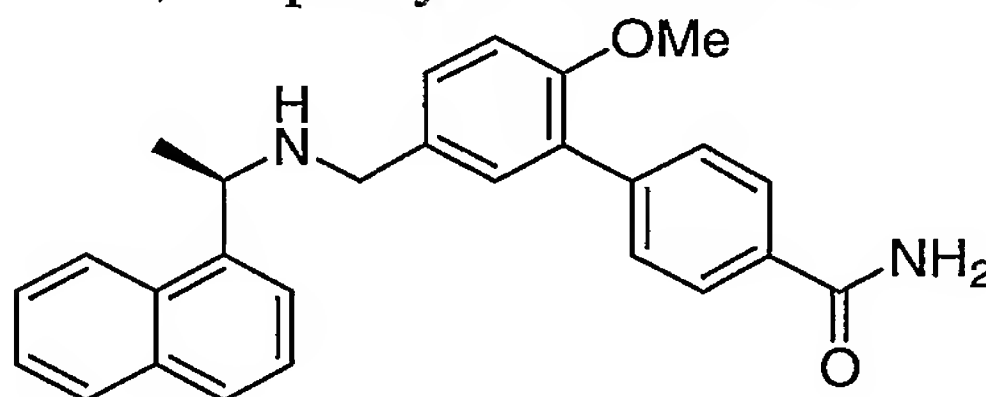
15

MW 418.534  
Mass found: 286, 268, 441, 419

**Example 317**

20

N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide



25

MW 438.568  
Mass found: 268, 155, 461, 439

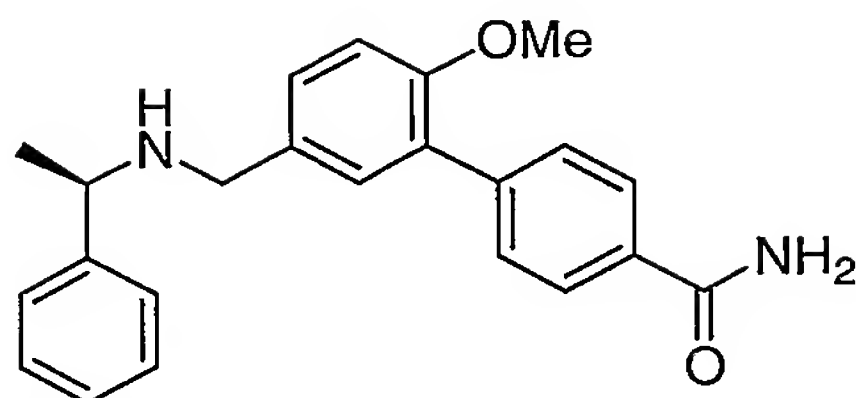
**Example 318**

30

N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide



- 200 -



MW 388.508

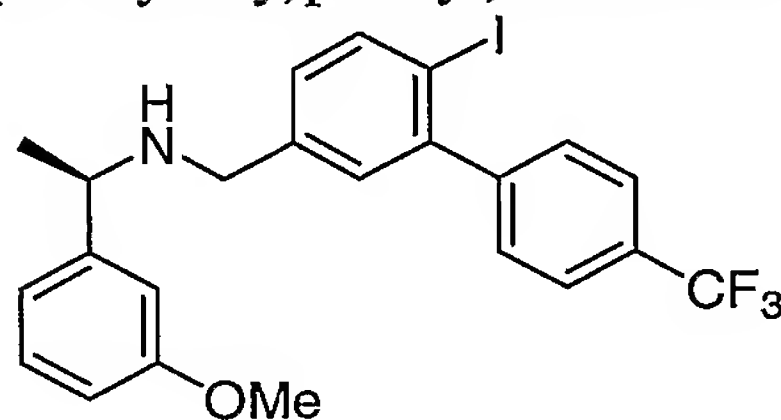
Mass found: 286, 268, 389, 411

5

**Example 319**

(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methoxy)phenyl)ethanamine

10



MW 511.319

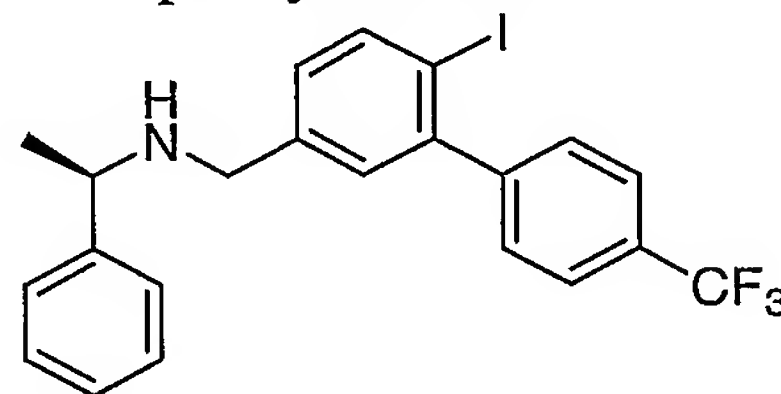
Mass found: 512, 402, 361

15

**Example 320**

(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

20



MW 481.293

Mass found: 482, 523

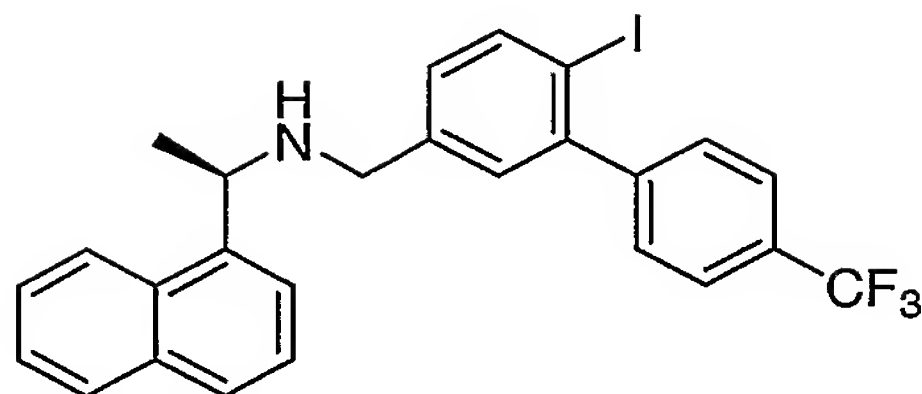
25

**Example 321**

(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 201 -

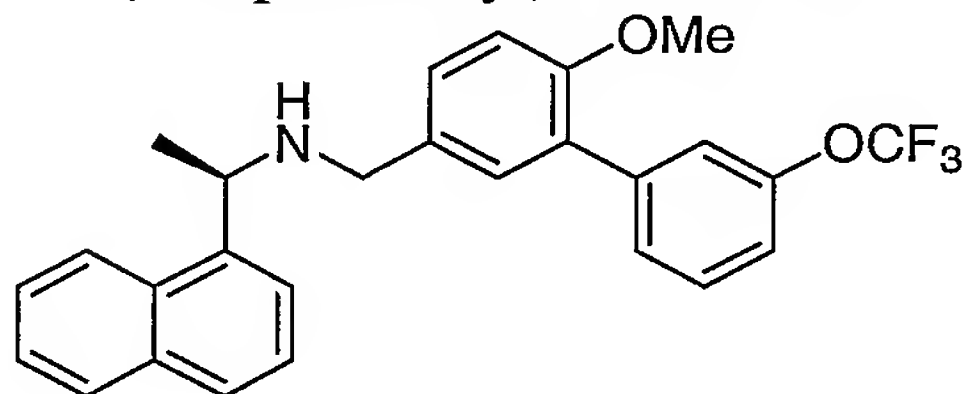


MW 531.353  
Mass found: 155, 532

5

**Example 322**

10 (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

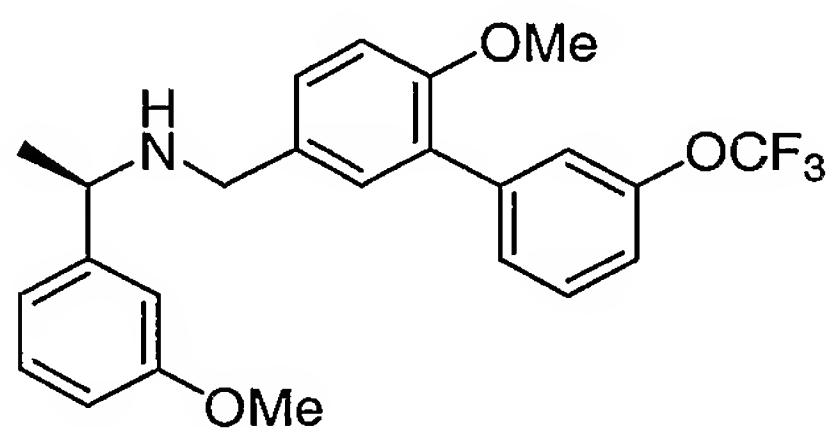


MW 451.486  
Mass found: 155, 452, 281

15

**Example 323**

20 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine



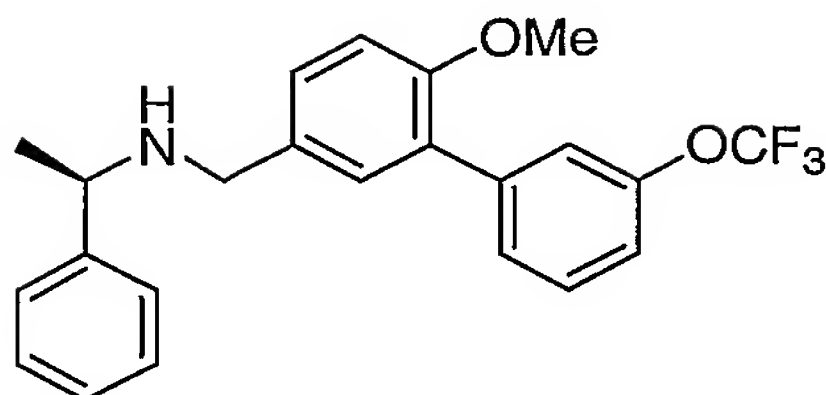
MW 431.452  
Mass found: 432, 281

25

**Example 324**

30 (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

- 202 -



MW 401.426

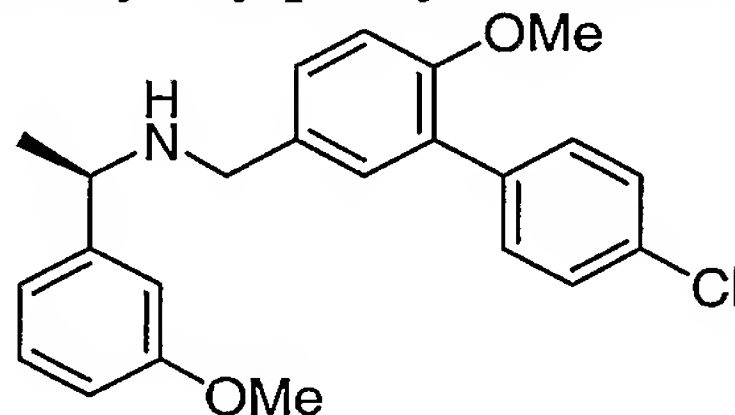
Mass found: 281, 402

5

**Example 325**

(1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



MW 381.901

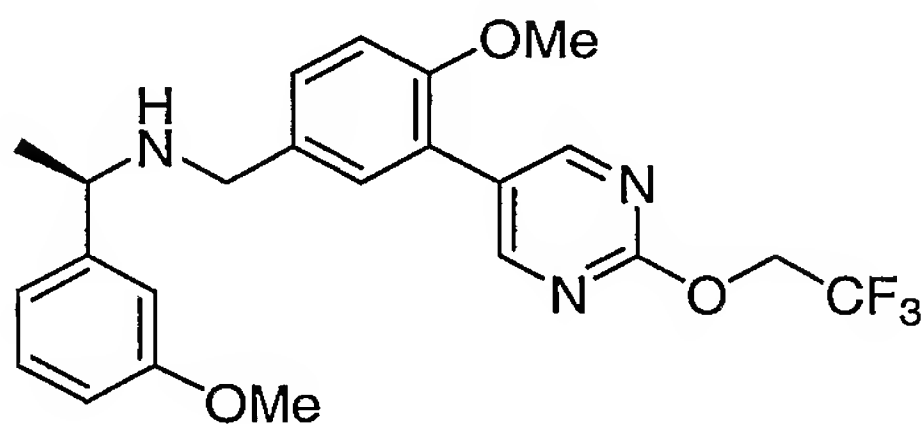
Mass found: 231, 382

15

**Example 326**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)ethanamine

20



MW 447.455

Mass found: 448

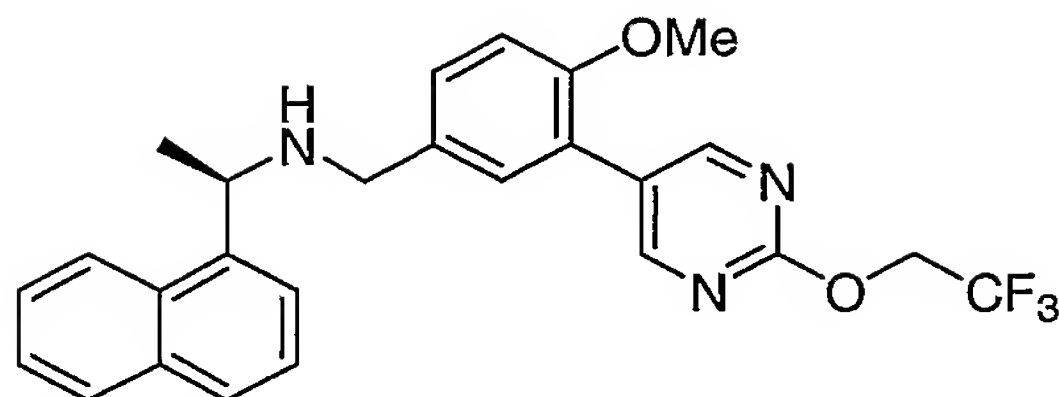
25

**Example 327**

(1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 203 -



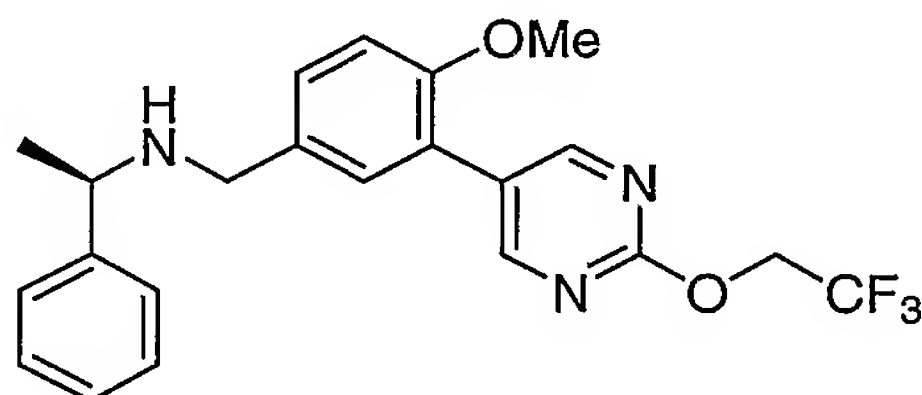
MW 467.489  
Mass found: 155, 468

5

**Example 328**

(1R)-N-((4-(methoxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)-1-phenylethanamine

10



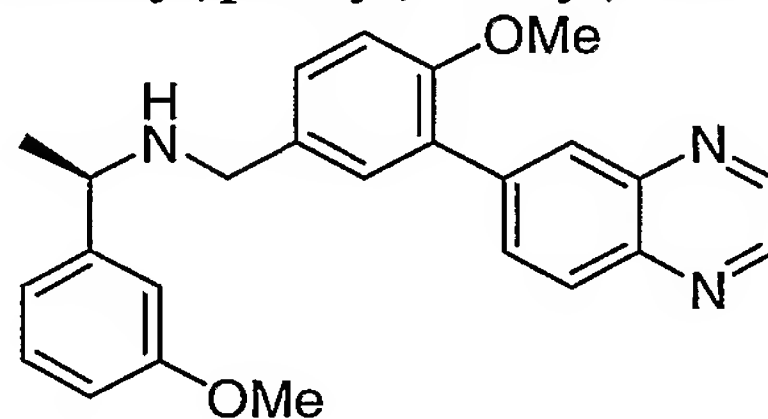
MW 417.429  
Mass found: 418, 297

15

**Example 329**

(1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(6-quinoxaliny)phenyl)methyl)ethanamine

20



MW 399.491  
Mass found: 249, 400

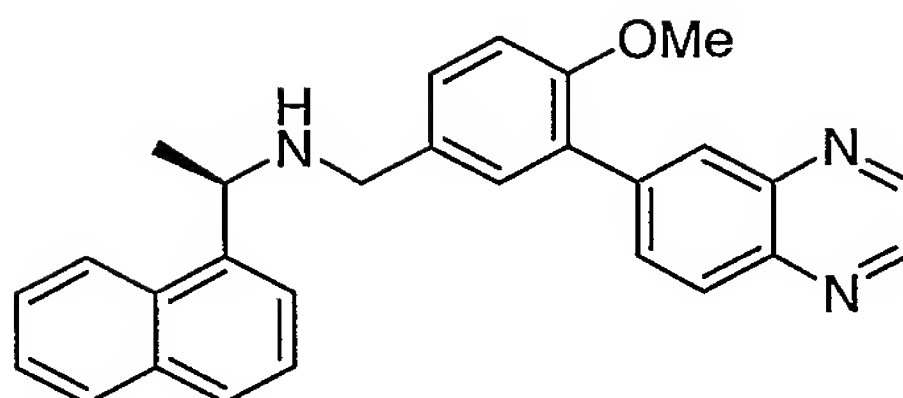
25

**Example 330**

(1R)-N-((4-(methoxy)-3-(6-quinoxaliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 204 -

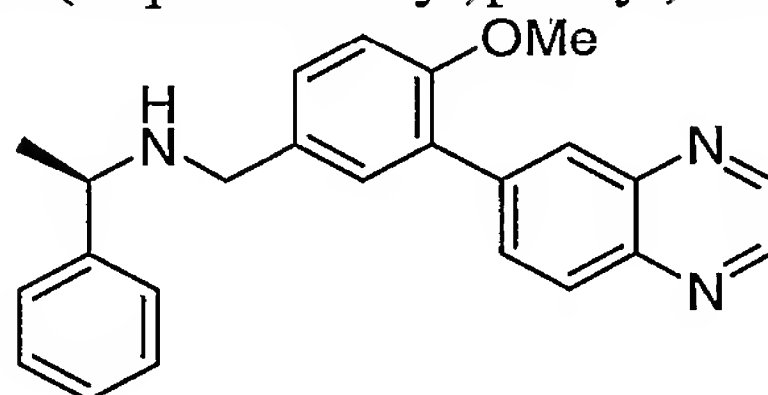


MW 419.526  
Mass found: 420, 249, 155

5

**Example 331**

(1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-phenylethylamine



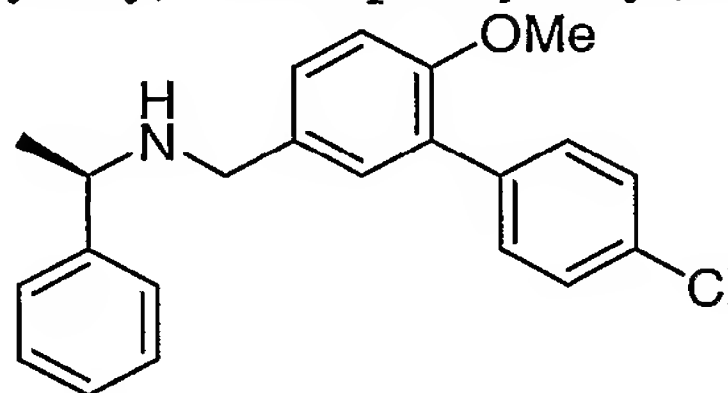
MW 369.466  
Mass found: 370, 249

10

15

**Example 332**

(1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethylamine



MW 351.875  
Mass found: 231, 352

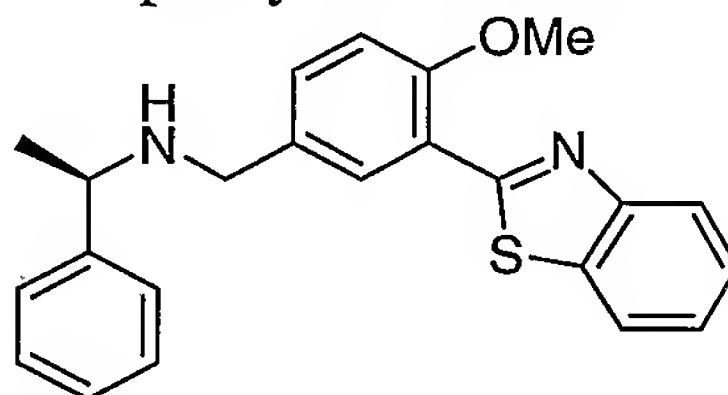
20

25

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**Example 333**

(1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

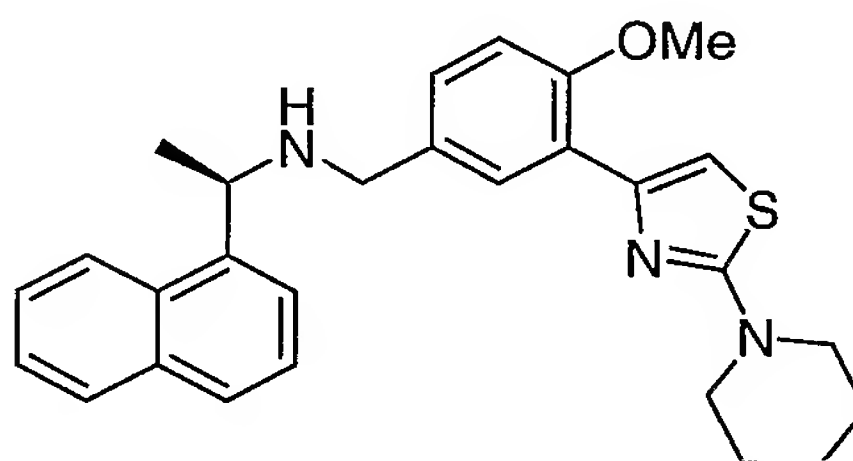


MW 374.506

Mass found: 375, 749

**Example 334**

(1R)-N-((4-(methyloxy)-3-(2-(1-piperidiny)-1,3-thiazol-4-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

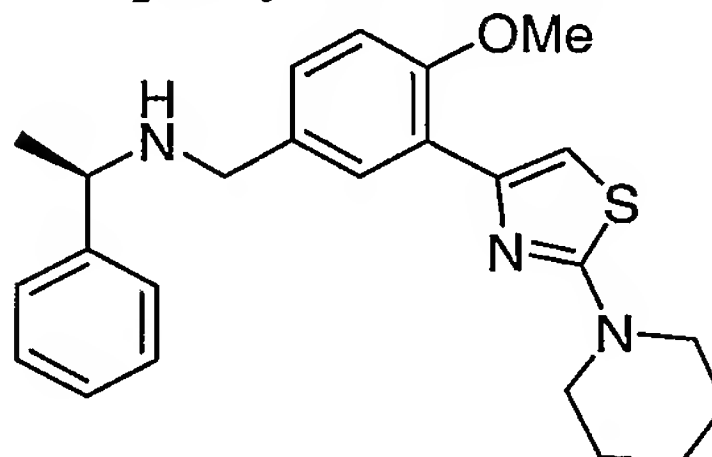


MW 457.639

Mass found: 458, 155

**Example 335**

(1R)-N-((4-(methyloxy)-3-(2-(1-piperidiny)-1,3-thiazol-4-yl)phenyl)methyl)-1-phenylethanamine



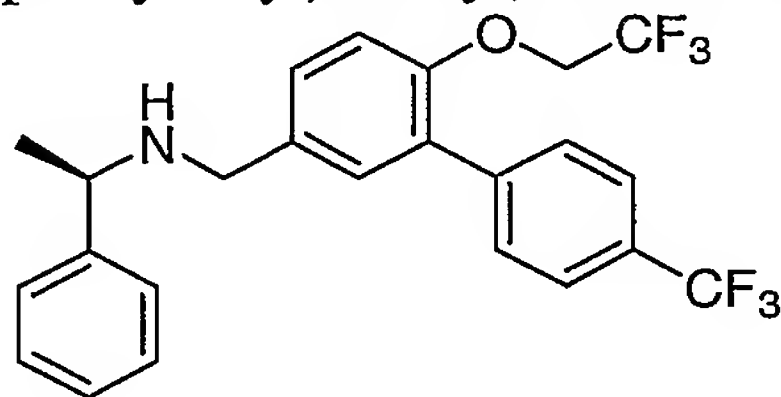
MW 407.579

Mass found: 408, 304

**Example 336**

- 206 -

(1R)-1-phenyl-N-((6-((2,2,2-trifluoroethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



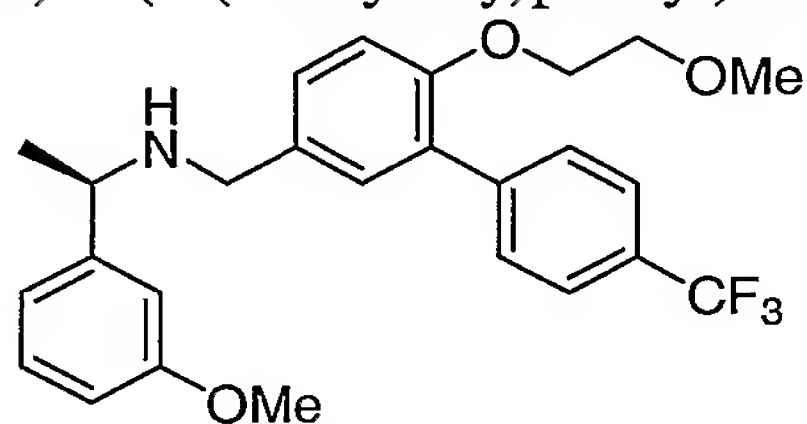
5

MW 453.424  
Mass found: 454, 333

**Example 337**

10

(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



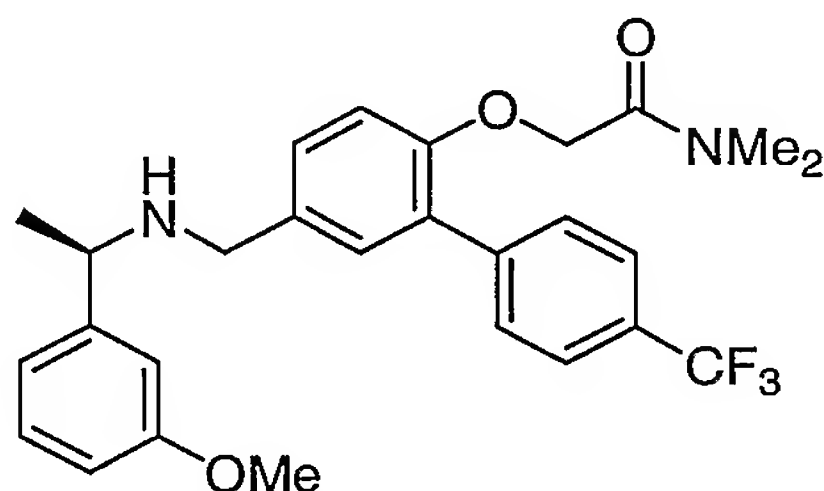
15

MW 459.505  
Mass found: 460, 309

**Example 338**

20

N,N-dimethyl-2-((5-(((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-4'-(trifluoromethyl)-1,1'-biphenyl-2-yl)oxy)acetamide



25

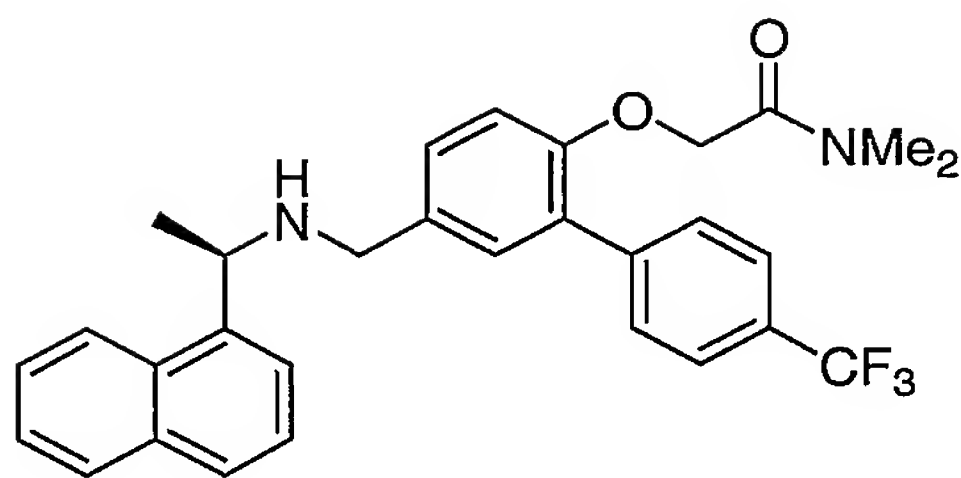
MW 486.531  
Mass found: 487, 336, 509

**Example 339**

30

N,N-dimethyl-2-((5-(((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-4'-(trifluoromethyl)-1,1'-biphenyl-2-yl)oxy)acetamide

- 207 -



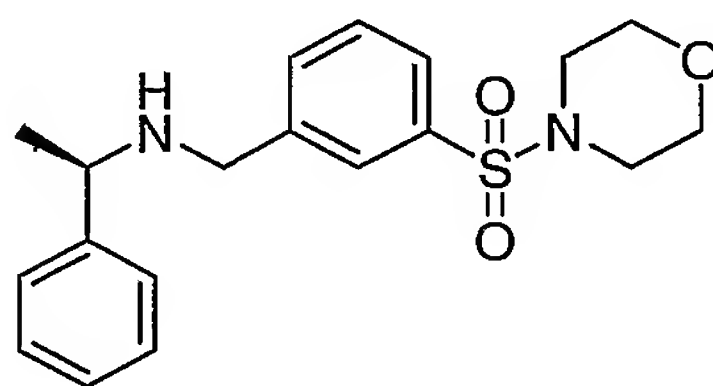
MW 506.565

Mass found: 507, 336, 529

5

**Example 340**

10 (1R)-N-((3-(4-morpholinesulfonyl)phenyl)methyl)-1-phenylethanamine



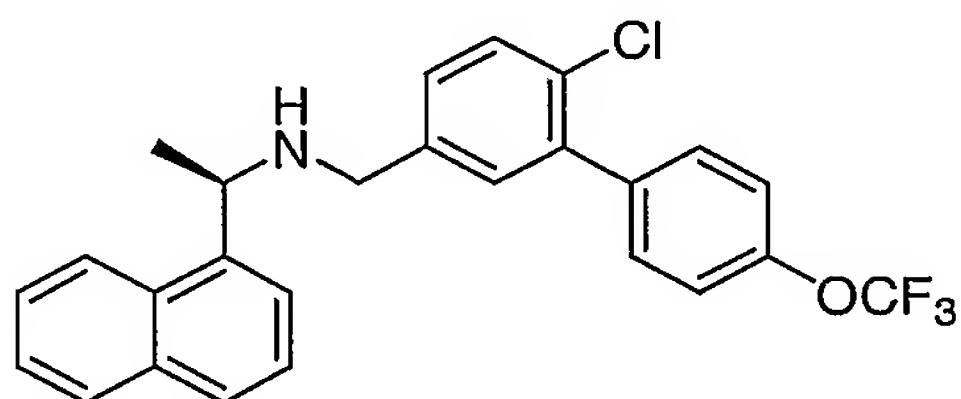
MW 360.476

Mass found: 298, 361, 402

15

**Example 341**

20 (1R)-N-((6-chloro-4'-((trifluoromethoxy)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



MW 455.905

Mass found: 456, 911

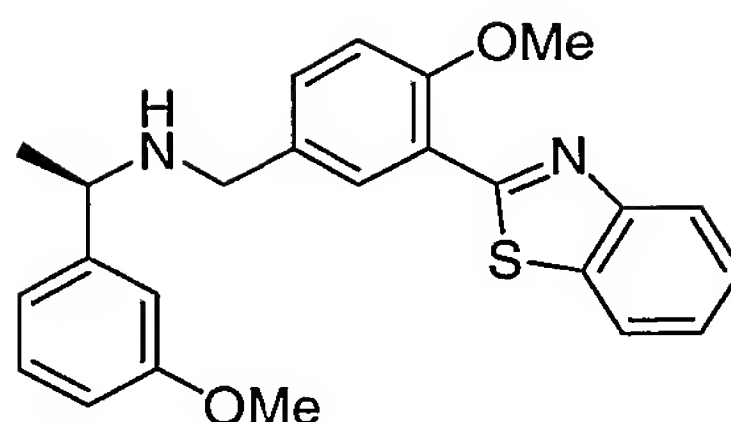
25

**Example 342**

30 (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methoxy)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



- 208 -



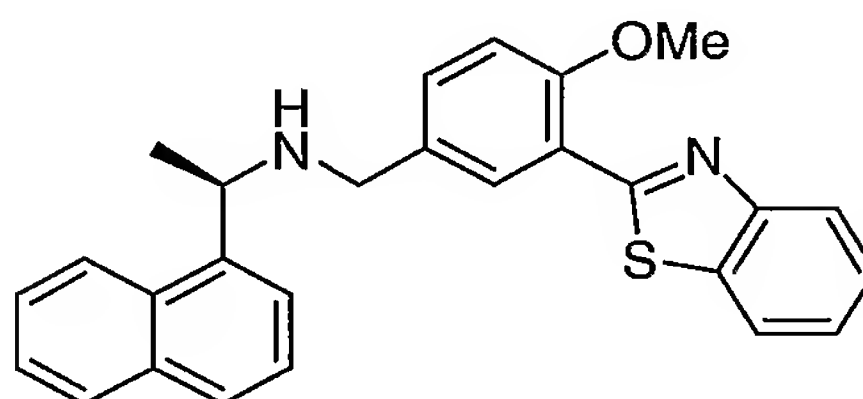
MW 404.532  
Mass found: 405, 809

5

**Example 343**

(1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

10



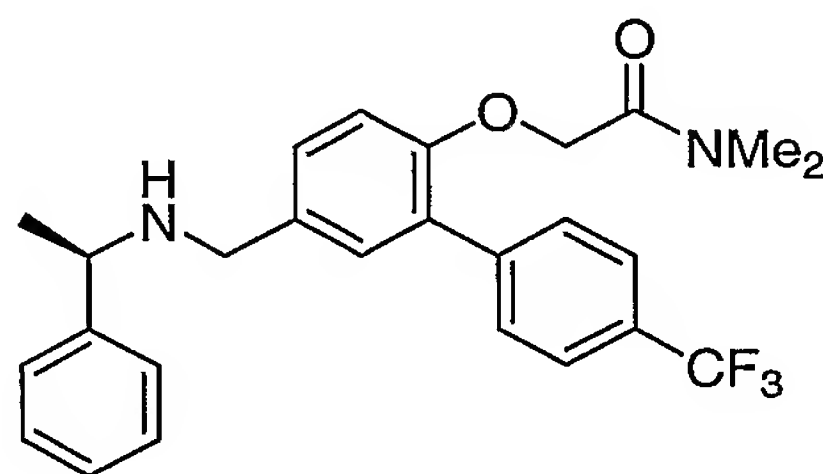
MW 424.566  
Mass found: 425, 849

15

**Example 344**

N,N-dimethyl-2-((5-(((1R)-1-phenylethyl)amino)methyl)-4'-(trifluoromethyl)-1,1'-biphenyl-2-yl)oxy)acetamide

20



MW 456.505  
Mass found: 336, 457, 354

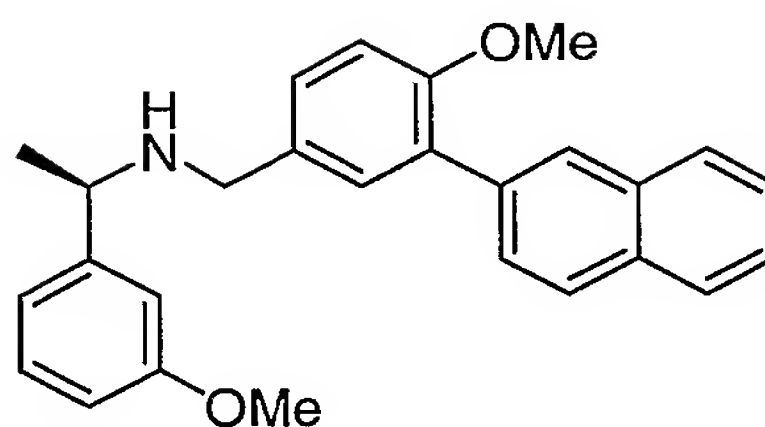
25

**Example 345**

(1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

30

- 209 -



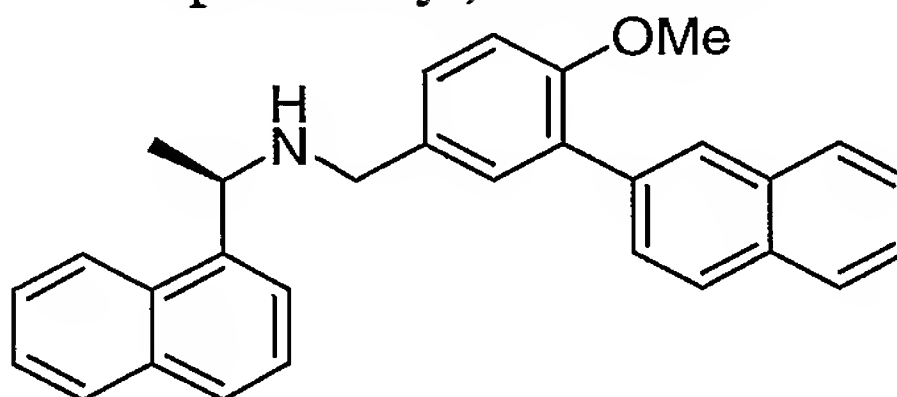
MW 433.98  
Mass found: 247, 398

5

**Example 346**

(1R)-N-((4-(methoxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

10

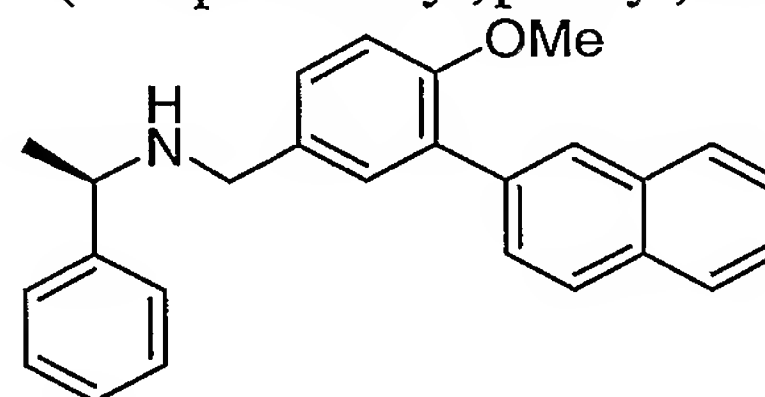


MW 454.02  
Mass found: 247, 155, 418

15

**Example 347**

(1R)-N-((4-(methoxy)-3-(2-naphthalenyl)phenyl)methyl)-1-phenylethanamine



20

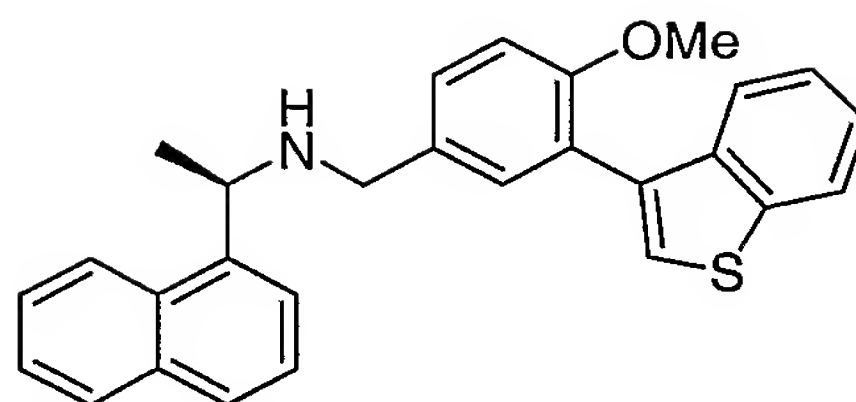
MW 403.96  
Mass found: 247, 368

25

**Example 348**

(1R)-N-((3-(1-benzothien-3-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

- 210 -



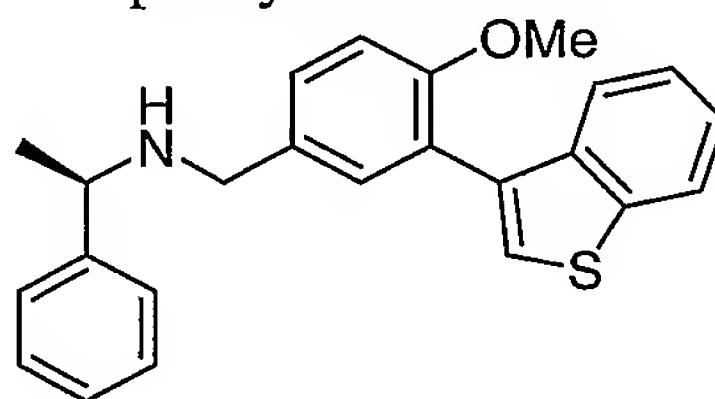
MW 460.04  
Mass found: 253, 155, 424

5

**Example 349**

(1R)-N-((3-(1-benzothiophen-3-yl)-4-(methoxy)phenyl)methyl)-1-phenylethanamine

10



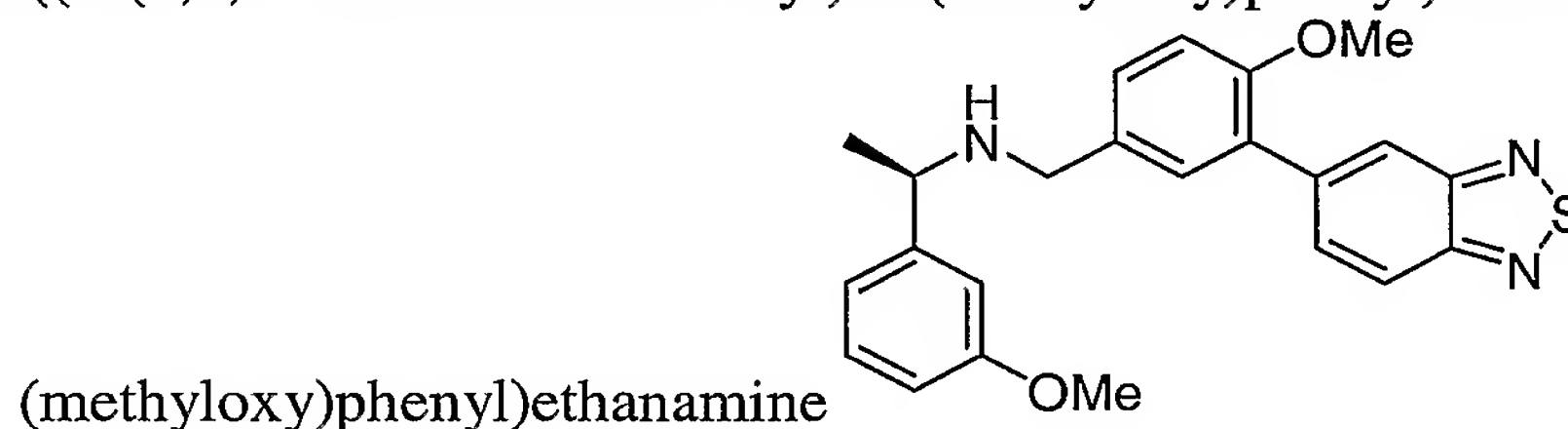
MW 409.98  
Mass found: 253, 374

15

**Example 350**

(1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methoxy)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine

20



MW 441.98  
Mass found: 273, 255, 406

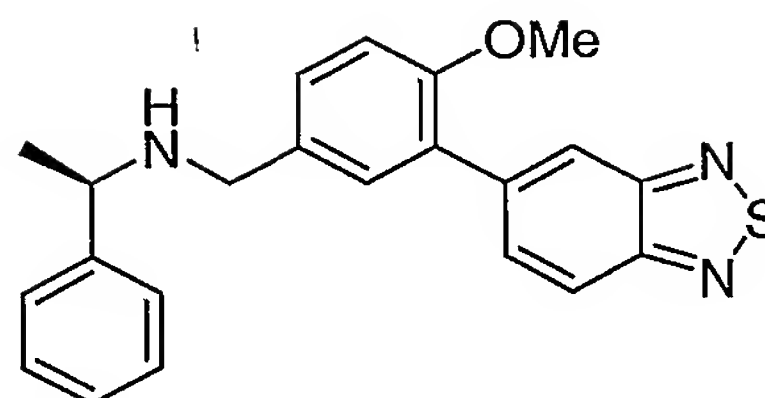
25

**Example 351**

(1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methoxy)phenyl)methyl)-1-phenylethanamine

30

- 211 -



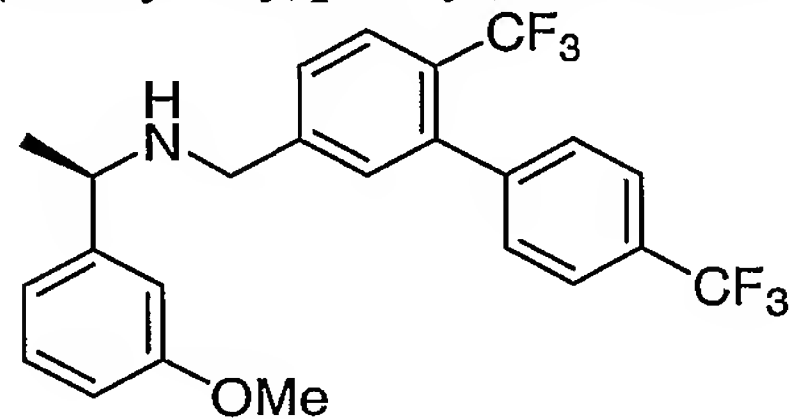
MW 411.96  
Mass found: 273, 255, 376

5

**Example 352**

(1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



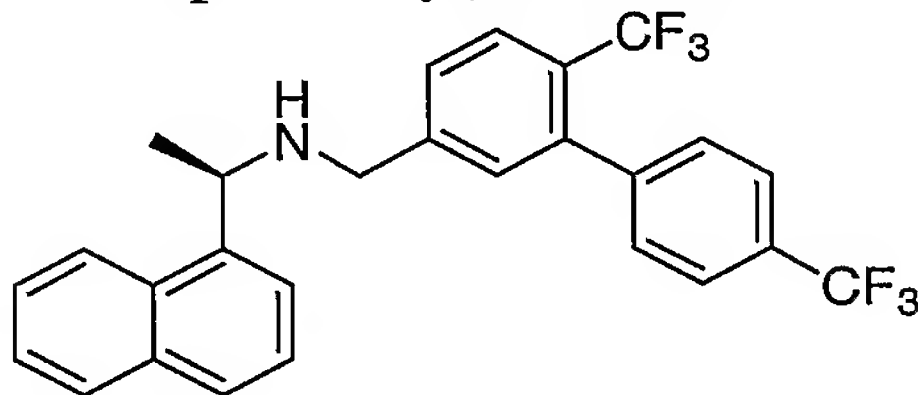
MW 489.89  
Mass found: 454, 361, 344

15

**Example 353**

(1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

20



MW 509.93  
Mass found: 155

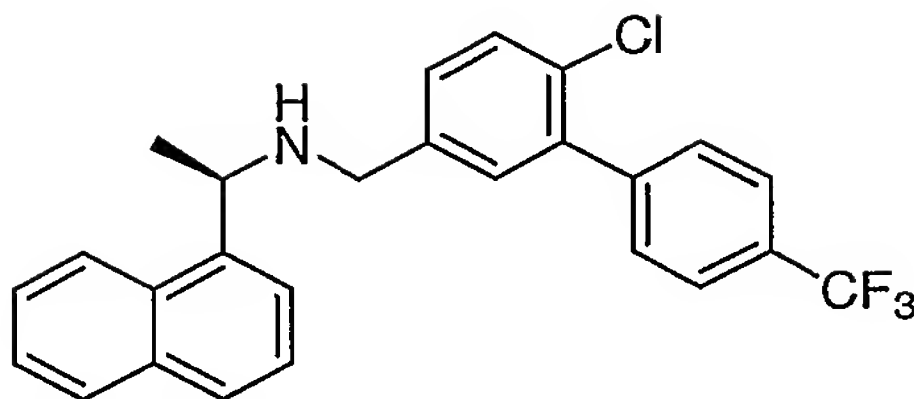
25

**Example 354**

(1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 212 -



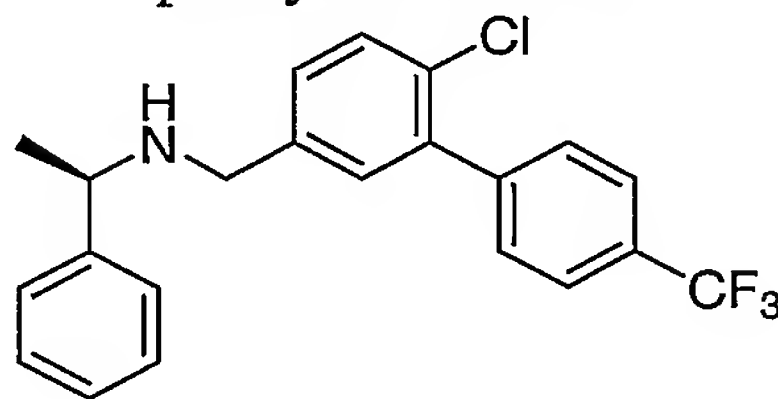
MW 439.91  
Mass found: 155

5

**Example 355**

(1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

10

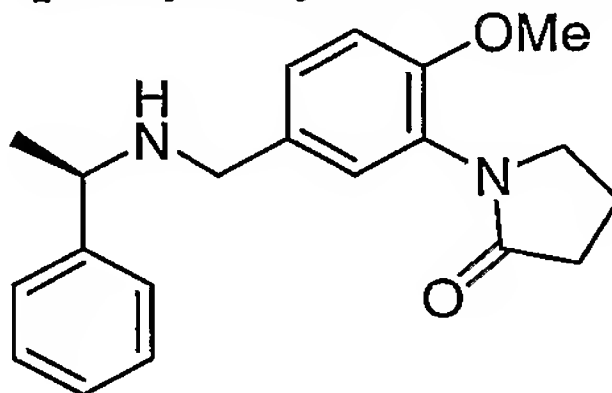


MW 389.95  
Mass found: 390, 269, 310

15

**Example 356**

1-(2-(methoxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyrrolidinone



20

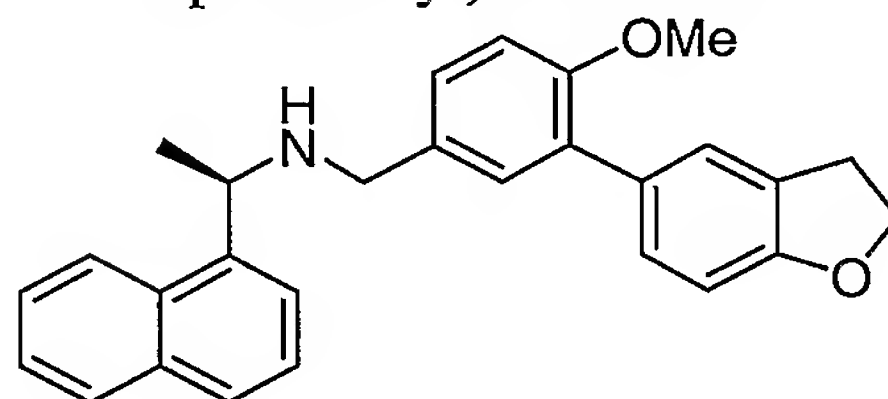
MW 324.43  
Mass found: 204, 347, 325

25

- 213 -

**Example 357**

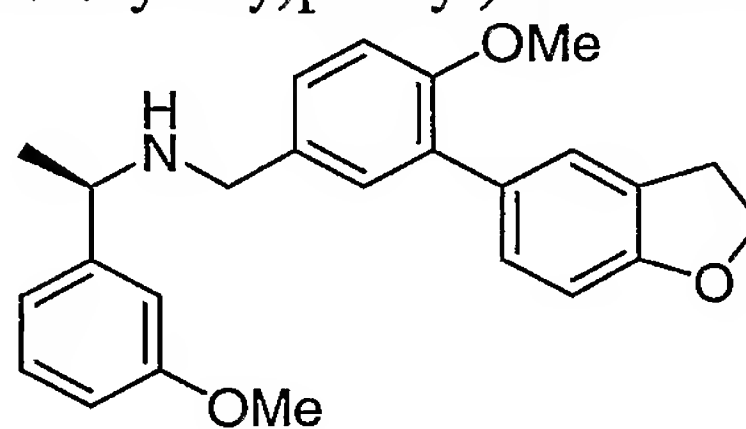
(1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



MW 409.53  
Mass found: 239, 410

**Example 358**

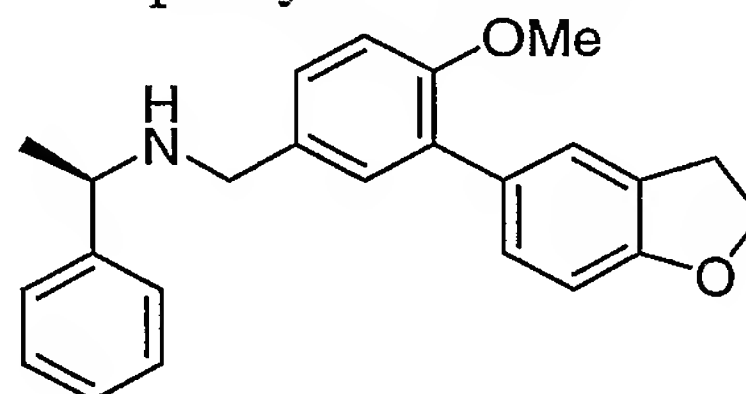
(1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



MW 389.50  
Mass found: 239, 390

**Example 359**

(1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

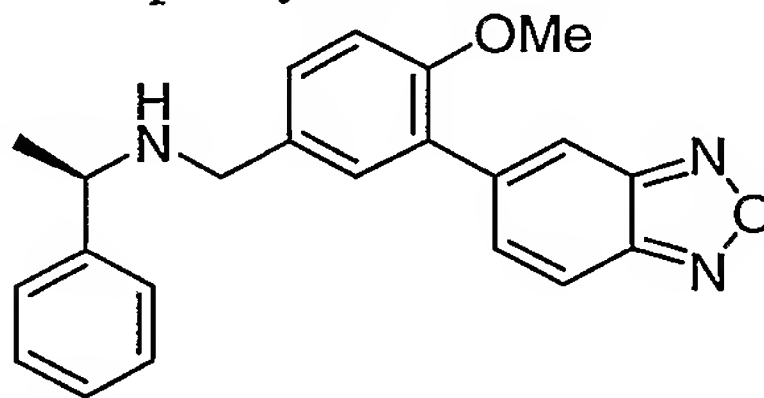


MW 359.47  
Mass found: 239, 360

**Example 360**

- 214 -

(1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



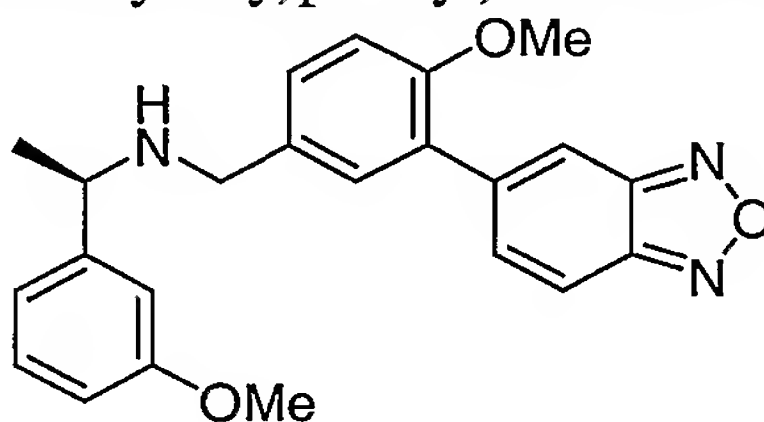
5

MW 359.43  
Mass found: 239, 360, 401

### Example 361

10

(1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



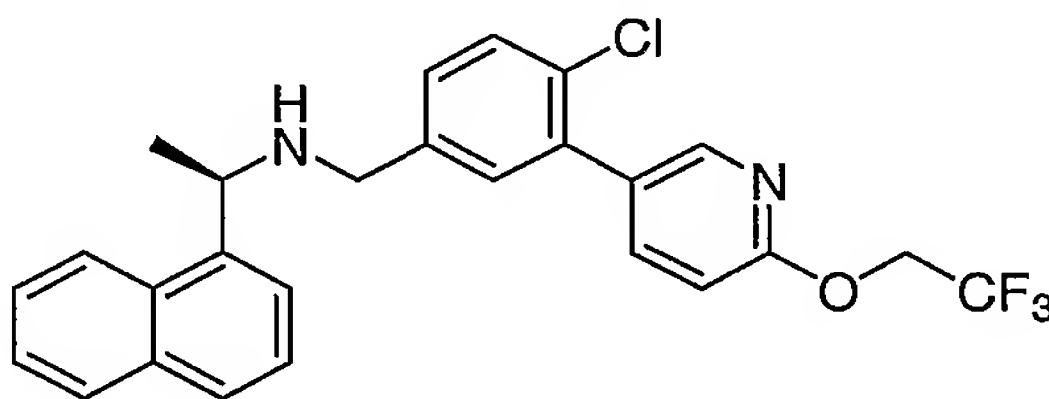
15

MW 389.46  
Mass found: 390, 431, 779

### Example 362

20

(1R)-N-((4-chloro-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



25

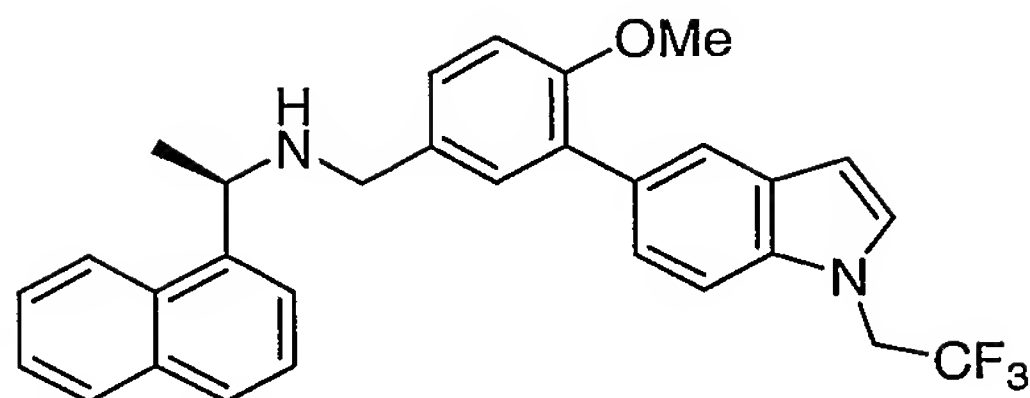
MW 470.93  
Mass found: 155, 472

30

### Example 363

(1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

- 215 -



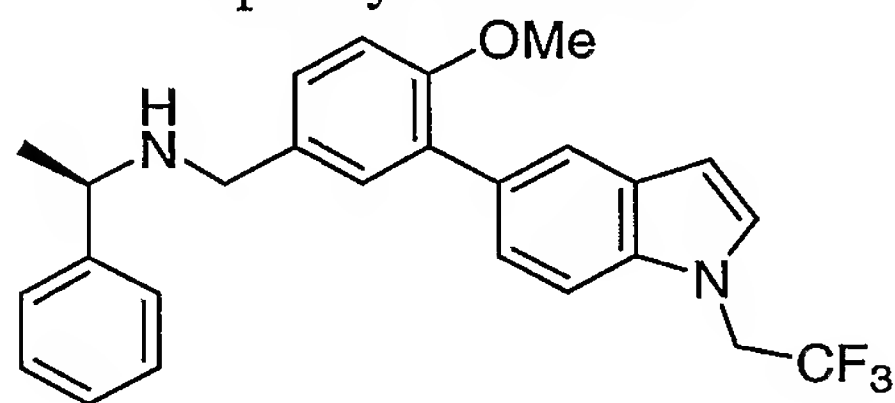
MW 488.55  
Mass found: 318, 489

5

**Example 364**

(1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-phenylethanamine

10



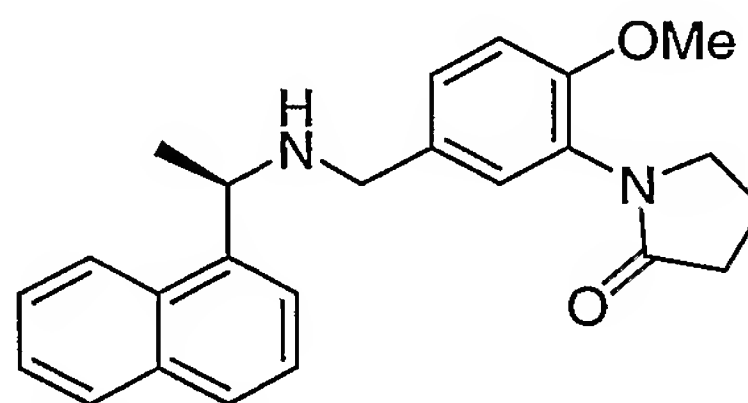
MW 438.491  
Mass found: 318, 439

15

**Example 365**

1-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyrrolidinone

20



MW 374.49  
Mass found: 240, 375, 397, 749

25

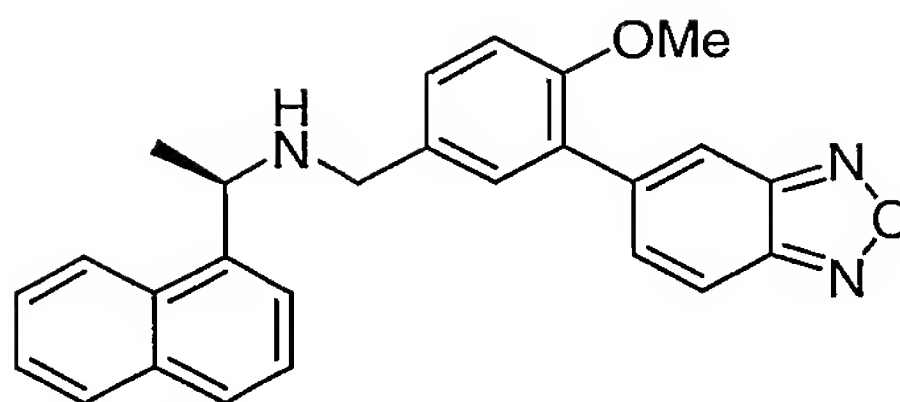
**Example 366**

(1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30



- 216 -



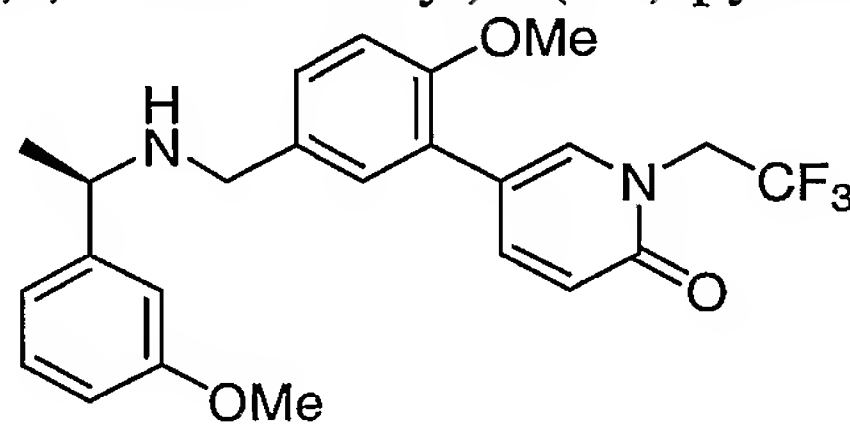
MW 409.49  
Mass found: 155, 410, 239

5

**Example 367**

5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-  
1-(2,2,2-trifluoroethyl)-2(1H)-pyridinone

10



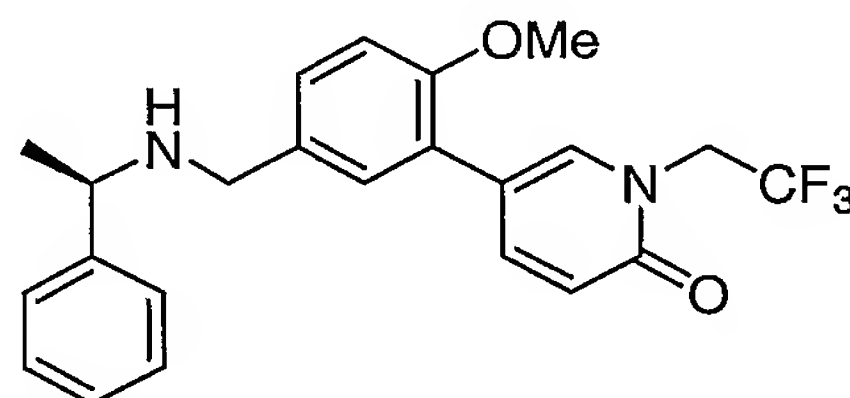
MW 446.466  
Mass found: 296, 447, 314

15

**Example 368**

5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1-(2,2,2-  
trifluoroethyl)-2(1H)-pyridinone

20



MW 416.441  
Mass found: 296, 314, 417

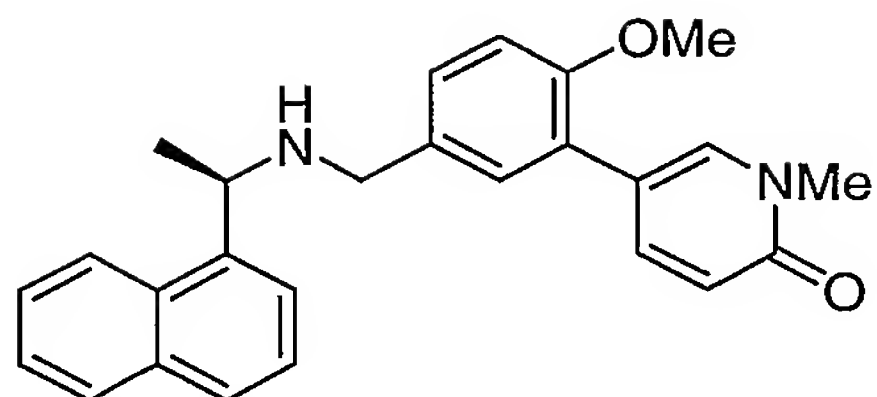
25

**Example 369**

1-methyl-5-(2-(methyloxy)-5-((((1R)-1-(1-  
naphthalenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone

30

- 217 -



MW 398.503

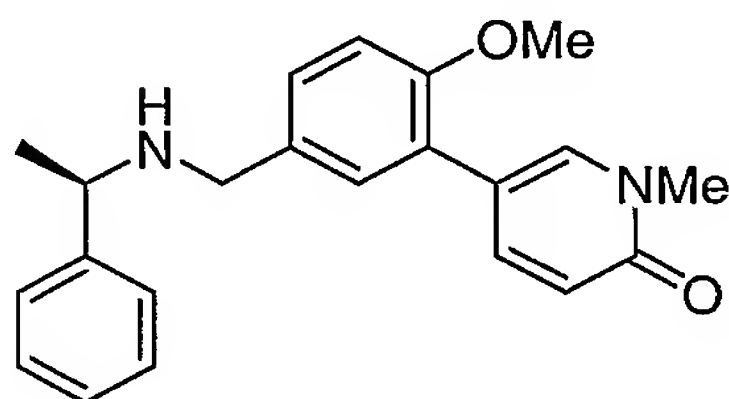
Mass found: 245, 399, 228, 155

5

**Example 370**

1-methyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-  
2(1H)-pyridinone

10



MW 348.444

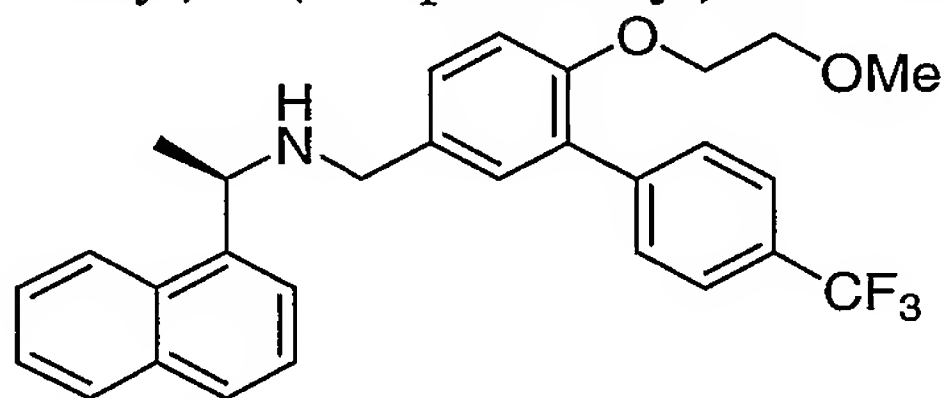
Mass found: 228, 349

15

**Example 371**

(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-  
yl)methyl)-1-(1-naphthalenyl)ethanamine

20



MW 479.539

Mass found: 480, 959

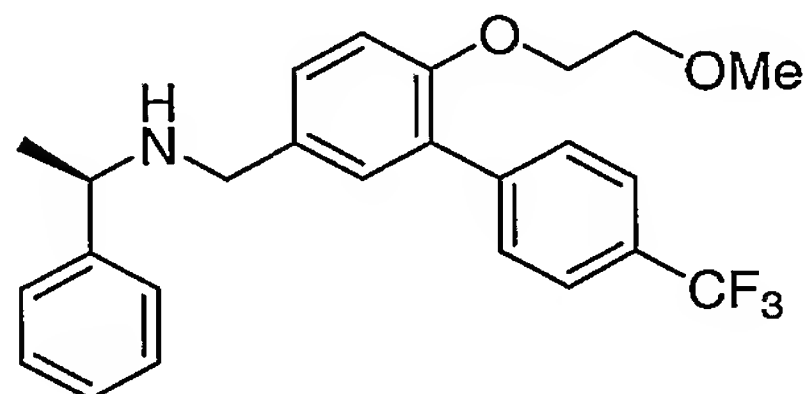
25

- 218 -

**Example 372**

(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

5



MW 429.479

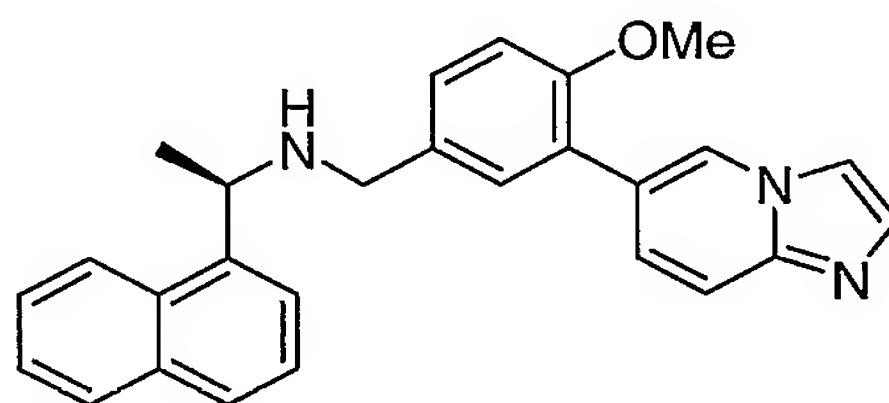
Mass found: 309, 430

10

**Example 373**

(1R)-N-((3-imidazo[1,2-a]pyridin-6-yl-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 407.514

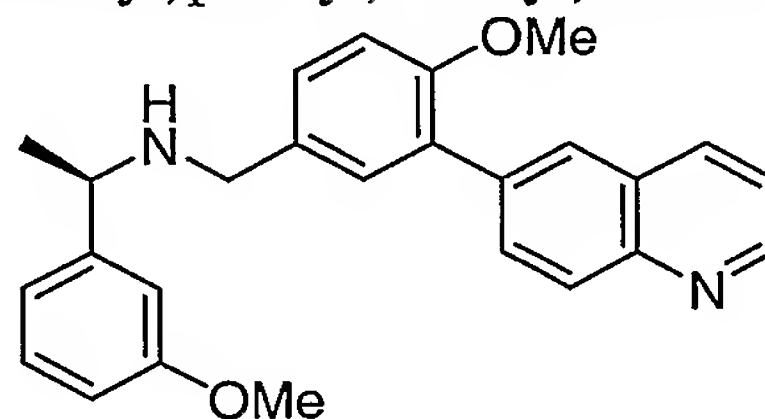
Mass found: 408, 254, 155

20

**Example 374**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)ethanamine

25



MW 398.503

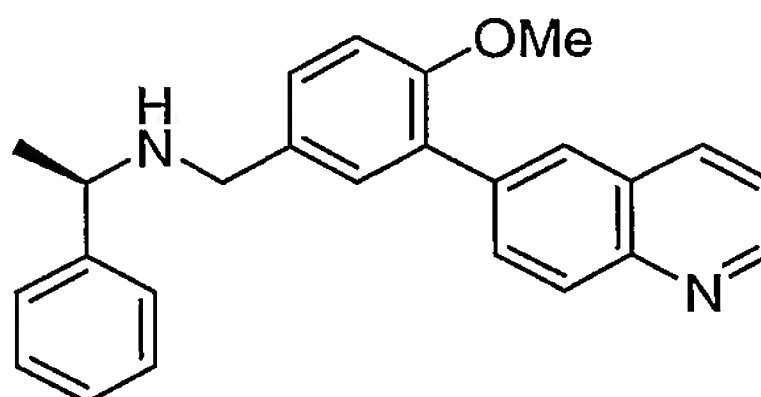
Mass found: 399, 248, 265

30

**Example 375**

- 219 -

(1R)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)-1-phenylethanamine



5

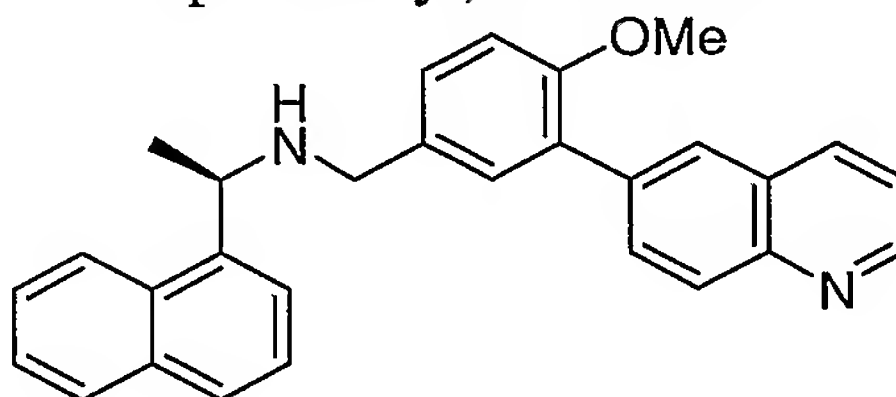
MW 368.478

Mass found: 248, 369, 265

10

**Example 376**

(1R)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



15

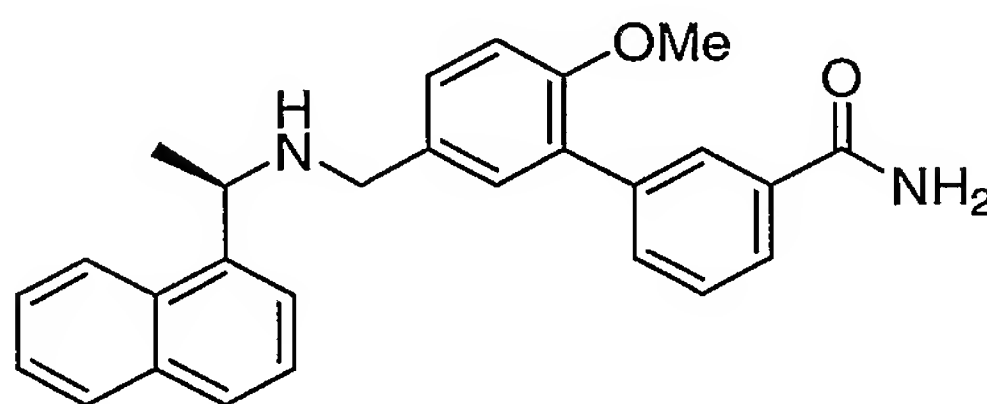
MW 418.537

Mass found: 419, 248, 265

20

**Example 377**

2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide



25

MW 410.514

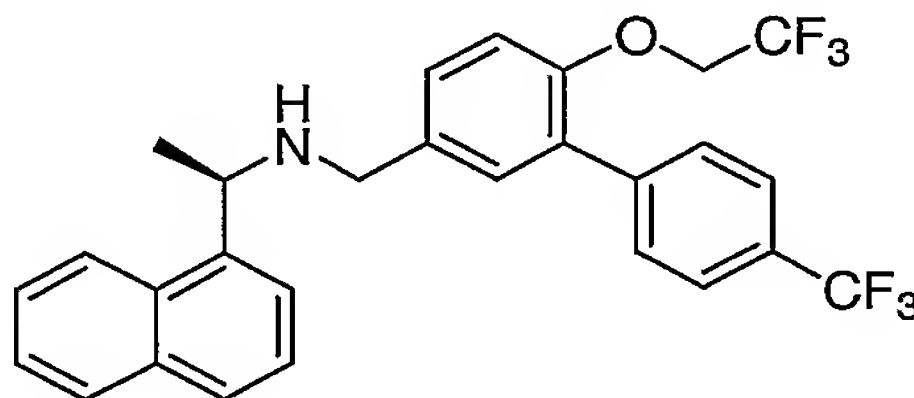
Mass found: 411, 821

30

**Example 378**

- 220 -

(1R)-1-(1-naphthalenyl)-N-((6-((2,2,2-trifluoroethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



5

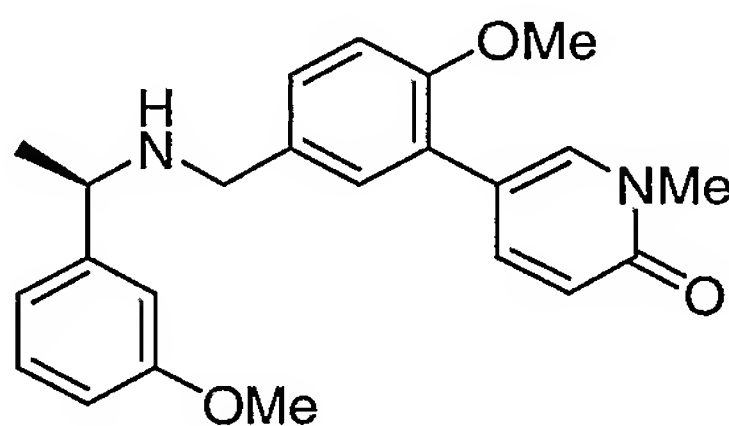
MW 503.484

Mass found: 155, 504

10

**Example 379**

1-methyl-5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone



15

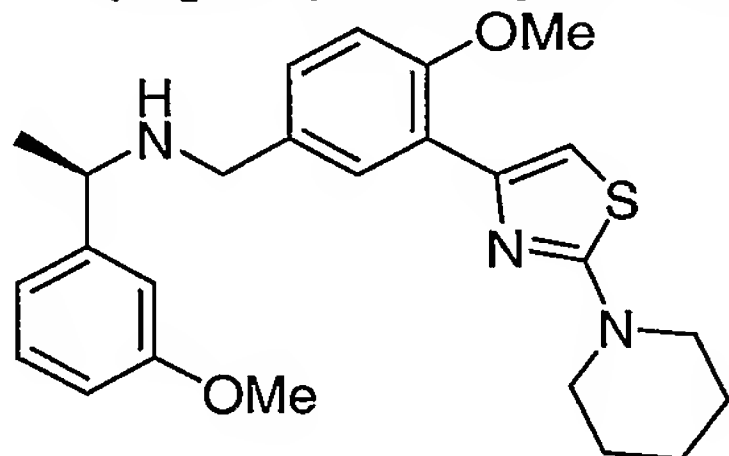
MW 378.469

Mass found: 228, 379

20

**Example 380**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-(1-piperidinyl)-1,3-thiazol-4-yl)phenyl)methyl)ethanamine



25

MW 437.605

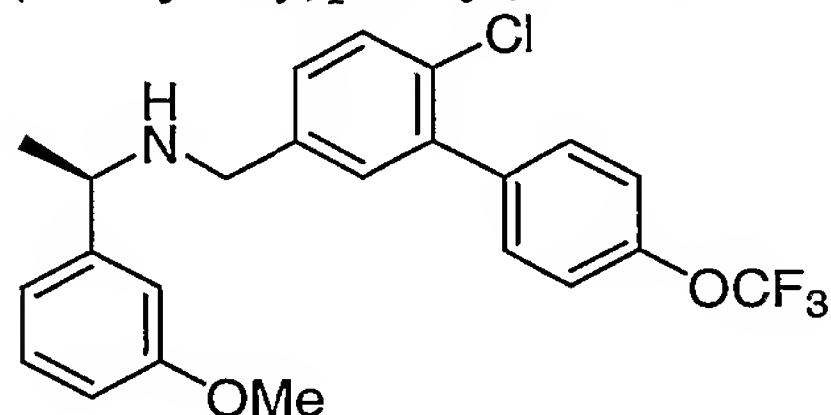
Mass found: 438, 875

30

**Example 381**

- 221 -

(1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methoxy)phenyl)ethanamine



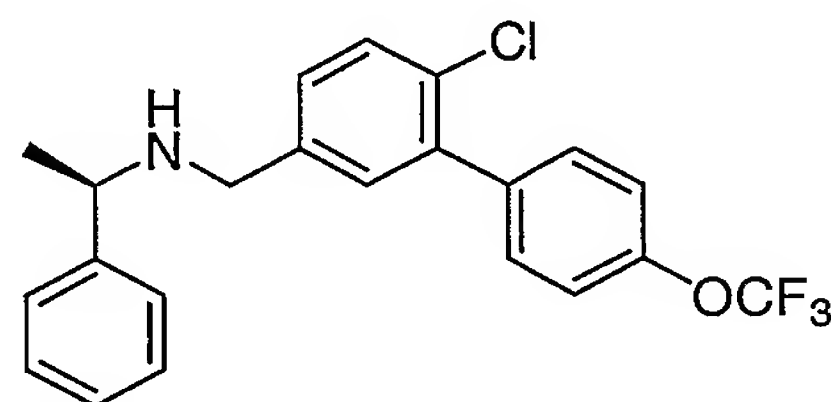
5

MW 435.871  
Mass found: 436, 477

### Example 382

10

(1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



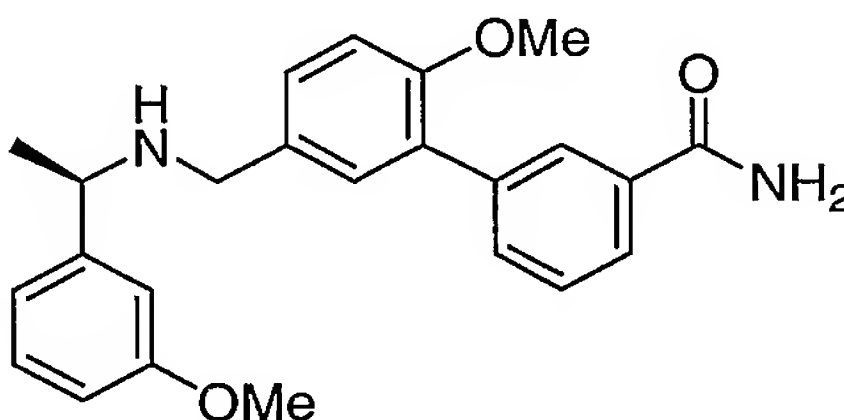
15

MW 405.845  
Mass found: 406

### Example 383

20

2'-(methoxy)-5'-((((1R)-1-(3-(methoxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide



25

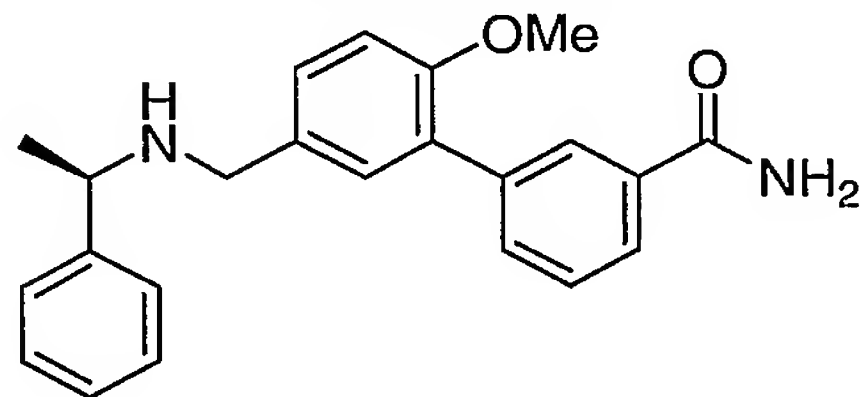
MW 390.48  
Mass found: 391, 432, 781, 895

### Example 384

30

- 222 -

2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide



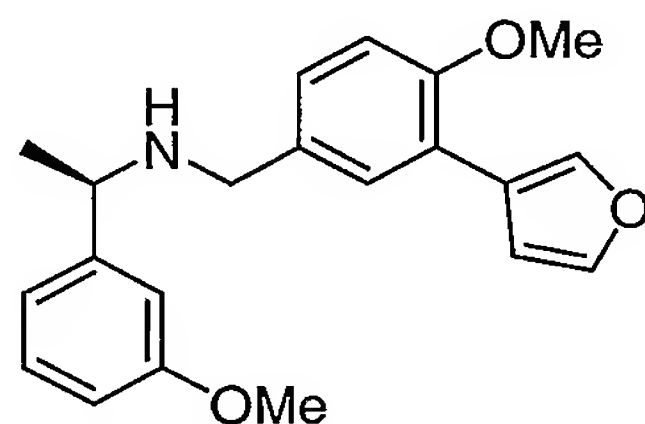
5

MW 360.455  
Mass found: 361, 721, 402

**Example 385**

10

(1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



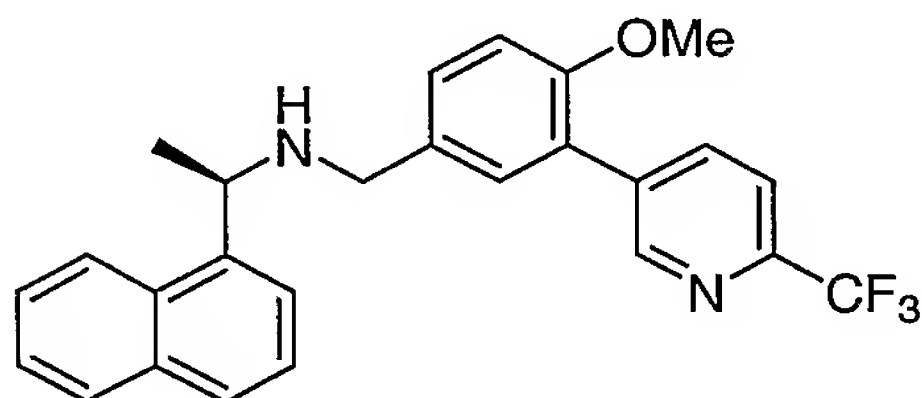
15

MW 337.417  
Mass found: 187, 338

**Example 386**

20

(1R)-1-(1-naphthalenyl)-N-((3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine



25

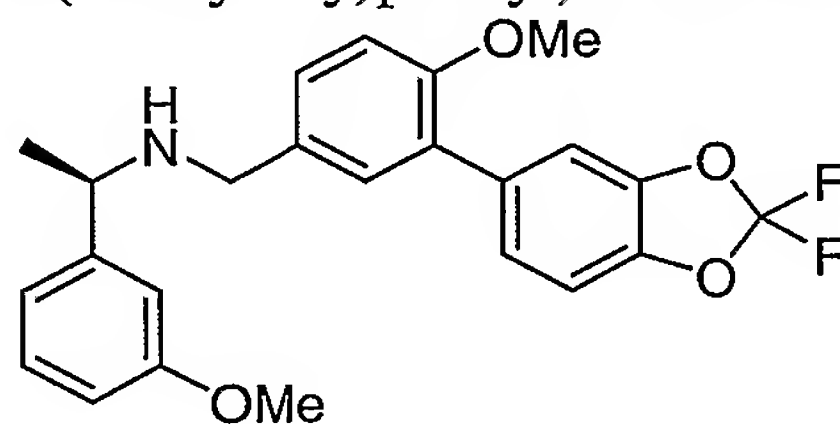
MW 406.449  
Mass found: 155, 407

30

- 223 -

**Example 387**

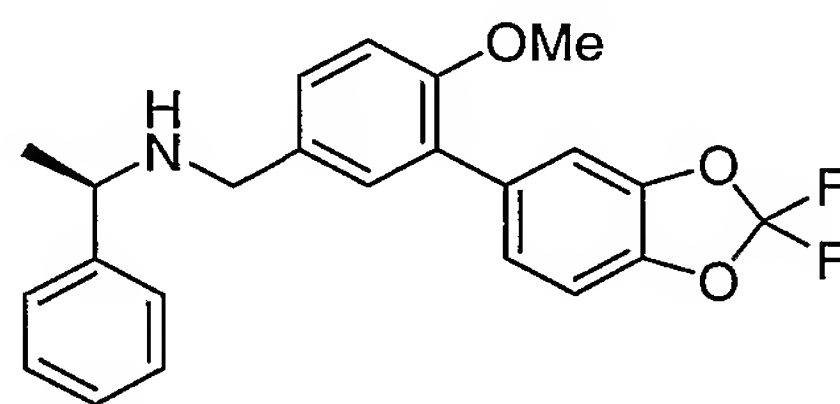
(1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methoxy)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



MW 427.445  
Mass found: 428, 855, 969

**Example 388**

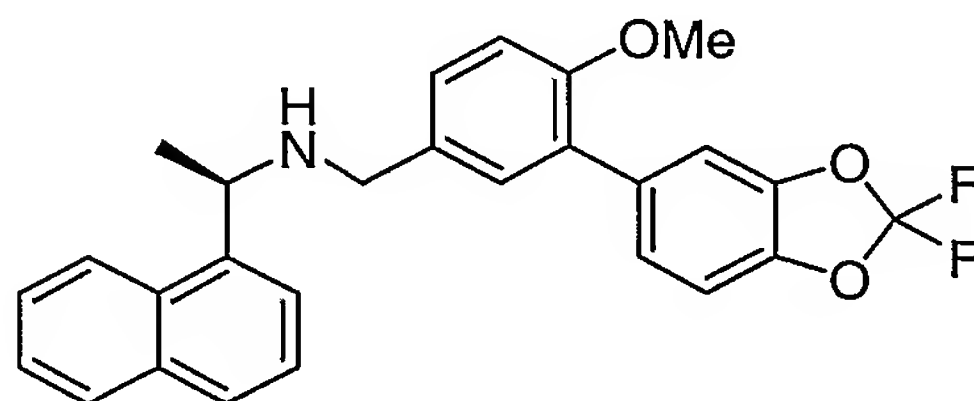
(1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methoxy)phenyl)methyl)-1-phenylethanamine



MW 397.419  
Mass found: 398, 277

**Example 389**

(1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



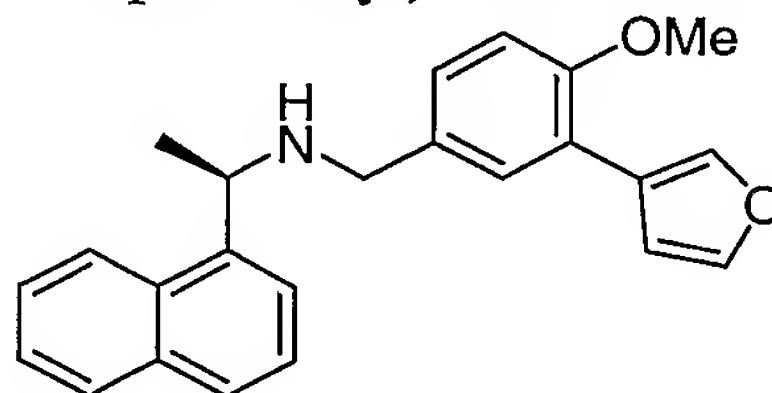
MW 447.479  
Mass found: 448, 895

**Example 390**



- 224 -

(1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



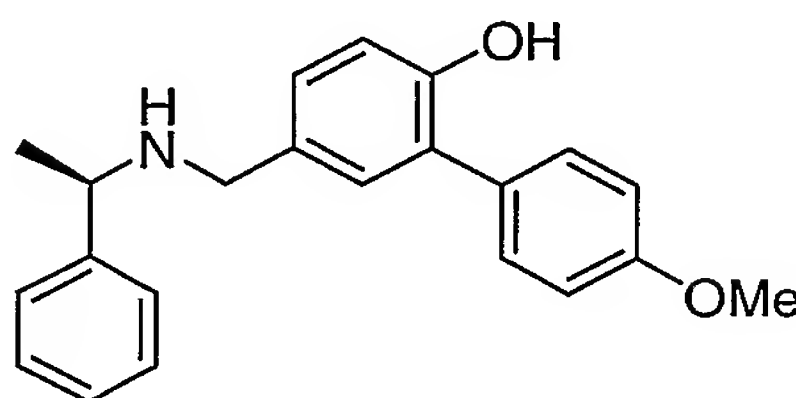
5

MW 357.451  
Mass found: 358

10

**Example 391**

4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-ol



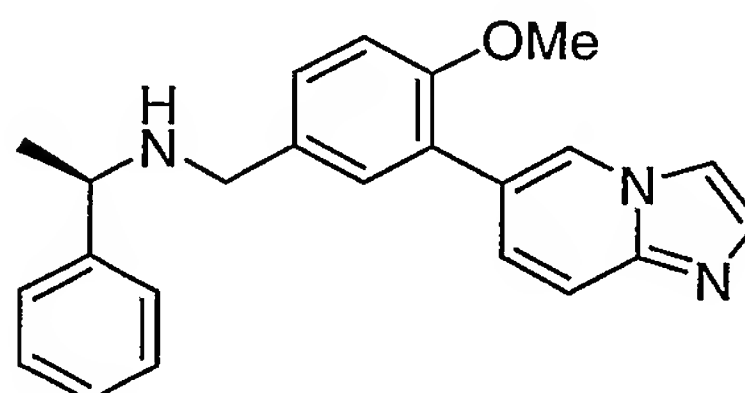
15

MW 333.429  
Mass found: 334, 213

20

**Example 392**

(1R)-N-((3-imidazo[1,2-a]pyridin-6-yl-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



25

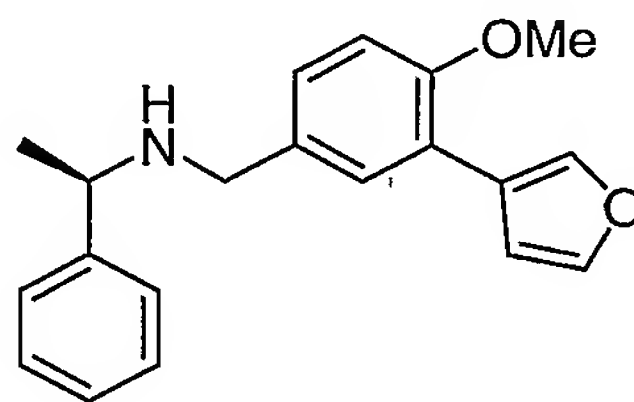
MW 357.455  
Mass found: 358

30

**Example 393**

- 225 -

(1R)-N-((3-(3-furanyl)-4-(methoxy)phenyl)methyl)-1-phenylethanamine

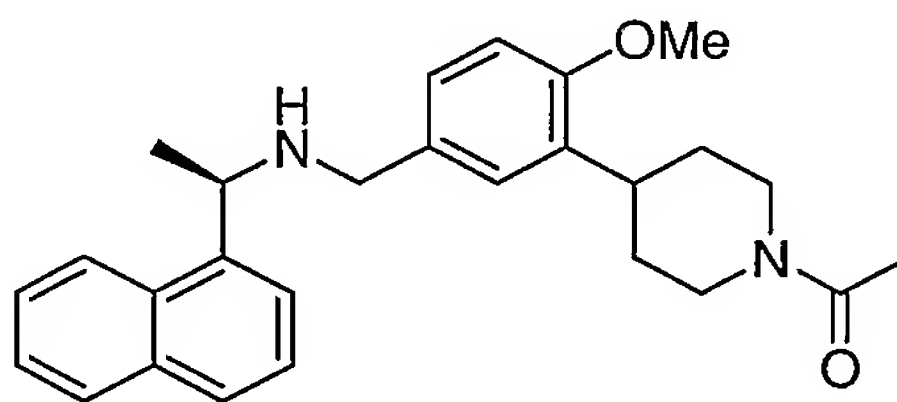


5

MW 307.391  
Mass found: 308, 187**Example 394**

10

(1R)-N-((3-(1-acetyl-4-piperidiny)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

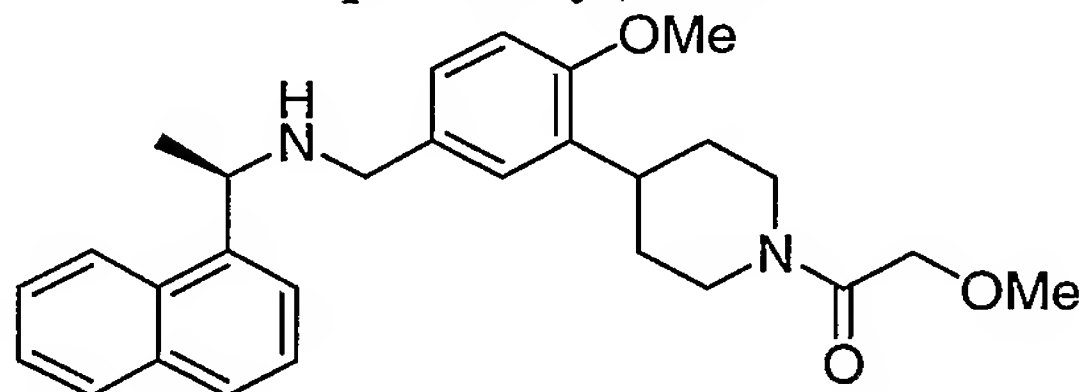


15

MW 416.562  
Mass found: 417**Example 395**

20

(1R)-N-((4-(methoxy)-3-(1-((methoxy)acetyl)-4-piperidiny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



25

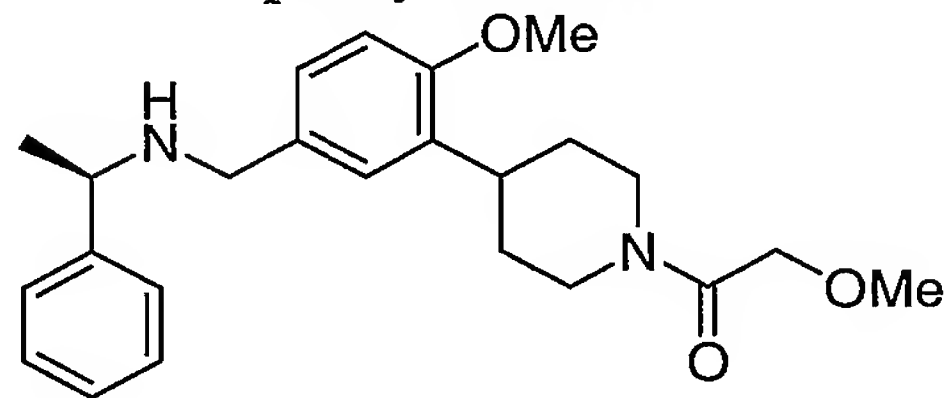
MW 446.588  
Mass found: 447

30

**Example 396**

- 226 -

(1R)-N-((4-(methyloxy)-3-(1-((methyloxy)acetyl)-4-piperidiny)phenyl)methyl)-1-phenylethanamine



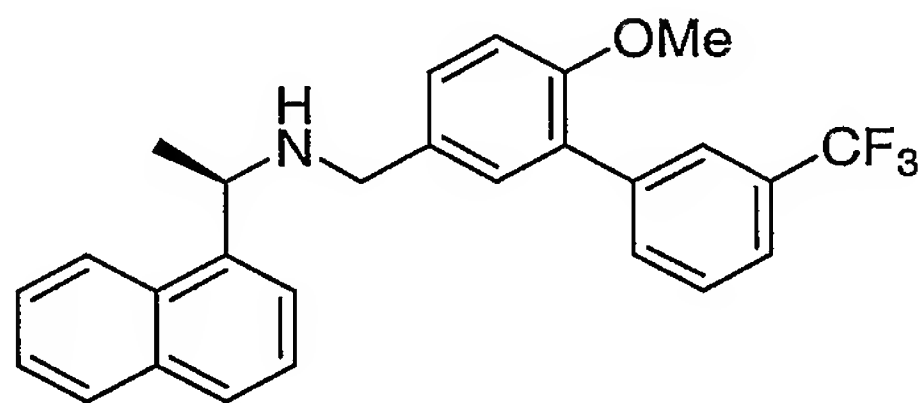
5

MW 396.528  
Mass found: 397

### Example 397

10

(1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



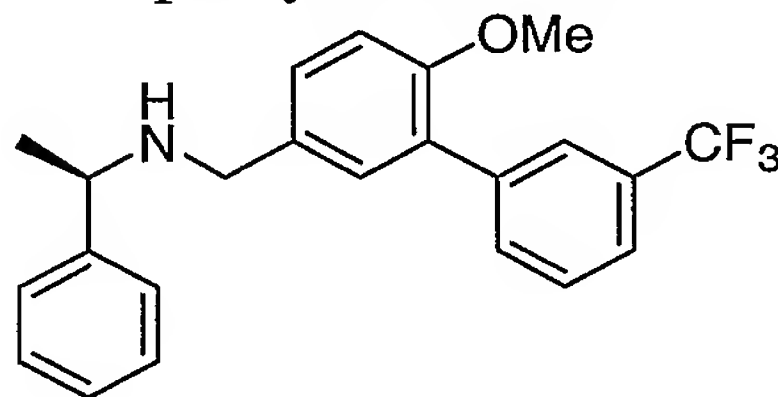
15

MW 435.487  
Mass found: 155, 436

20

### Example 398

(1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



25

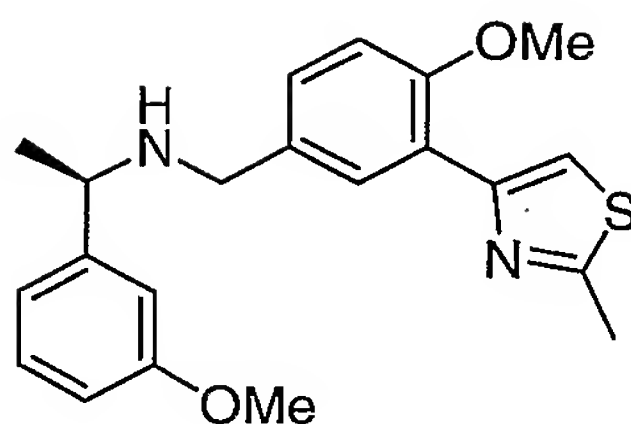
MW 385.427  
Mass found: 386, 265

30

### Example 399

(1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

- 227 -

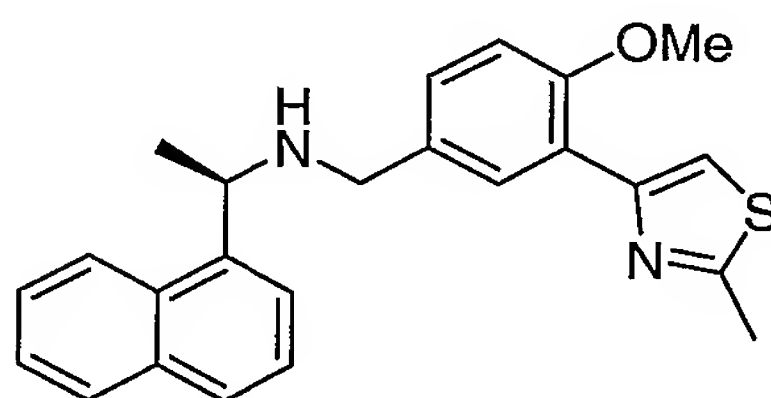


5

MW 368.499  
Mass found: 369, 218

**Example 400**

10 (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

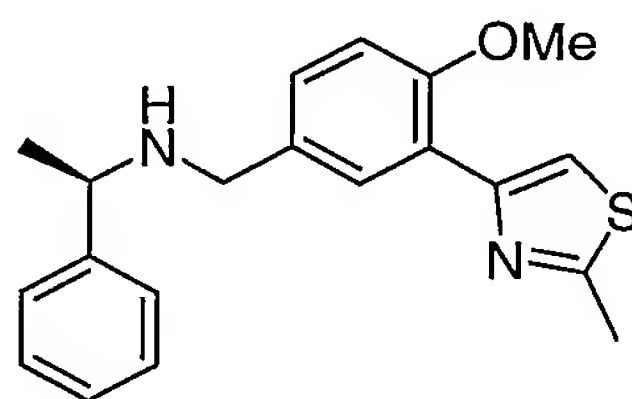


15

MW 388.533  
Mass found: 389, 218

**Example 401**

20 (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-phenylethanamine



25

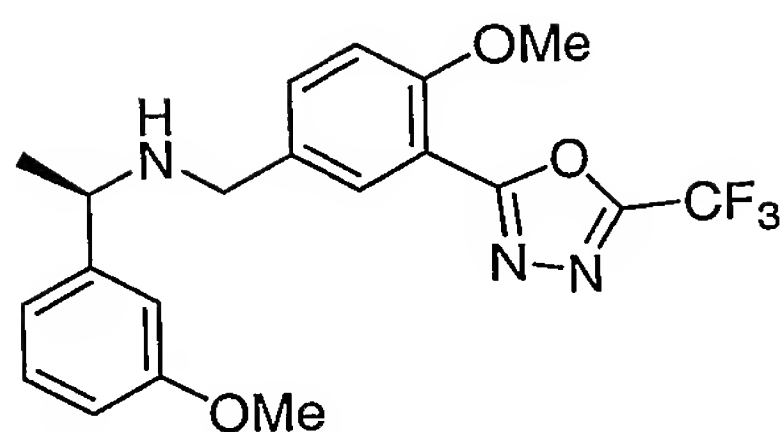
MW 338.473  
Mass found: 218, 339

30

**Example 402**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)ethanamine

- 228 -



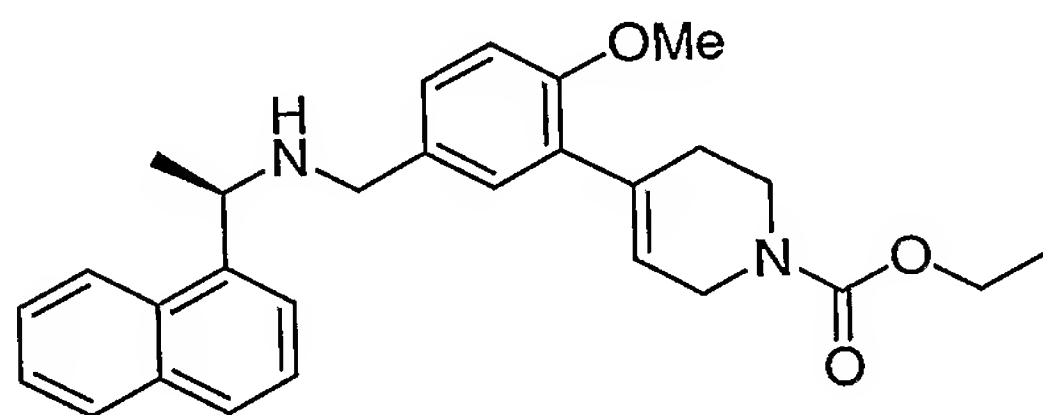
MW 407.39

Mass found: 408, 274

5

**Example 403**

10 ethyl 4-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-  
3,6-dihydro-1(2H)-pyridinecarboxylate



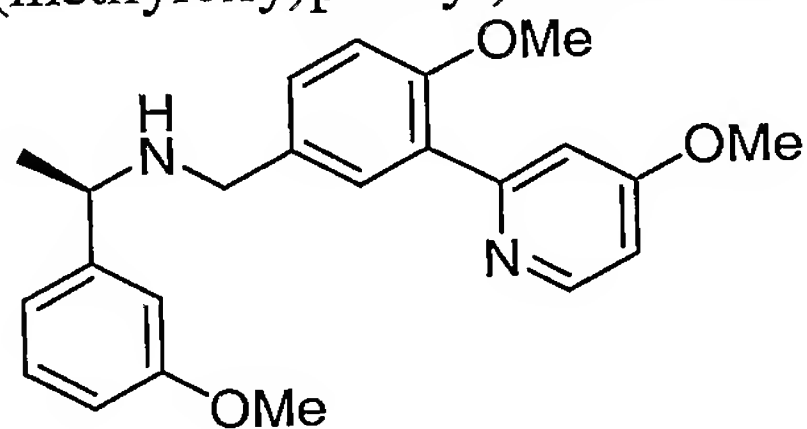
MW 444.572

Mass found: 445, 274, 155

15

**Example 404**

20 (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(3-  
(methyloxy)phenyl)ethanamine



MW 378.469

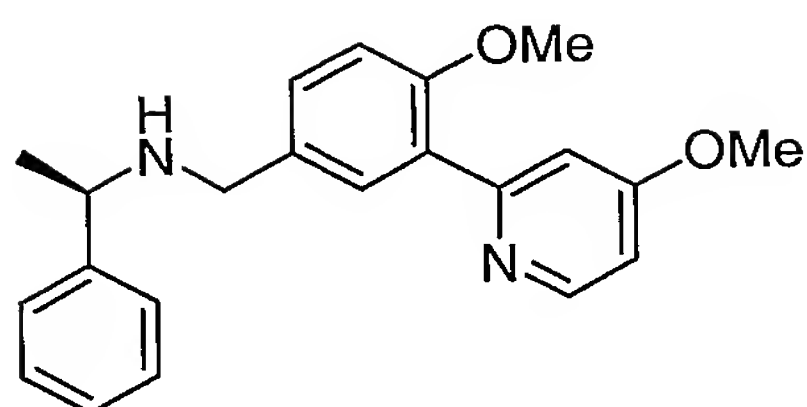
Mass found: 379

25

**Example 405**

30 (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-  
phenylethanamine

- 229 -



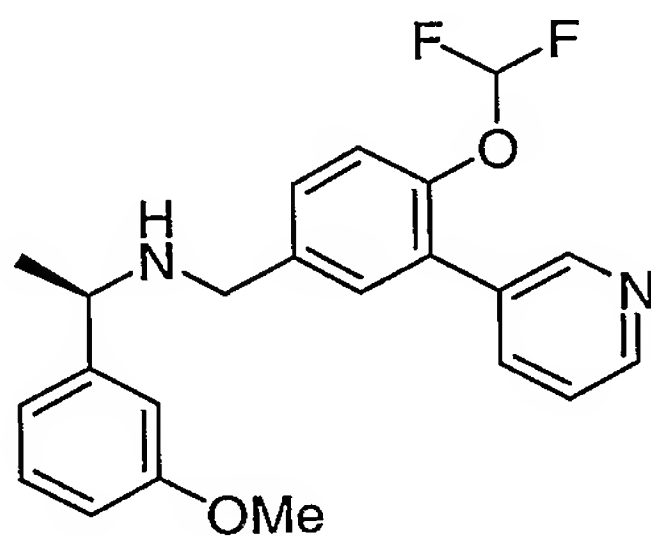
MW 348.444  
Mass found: 349

5

**Example 406**

(1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



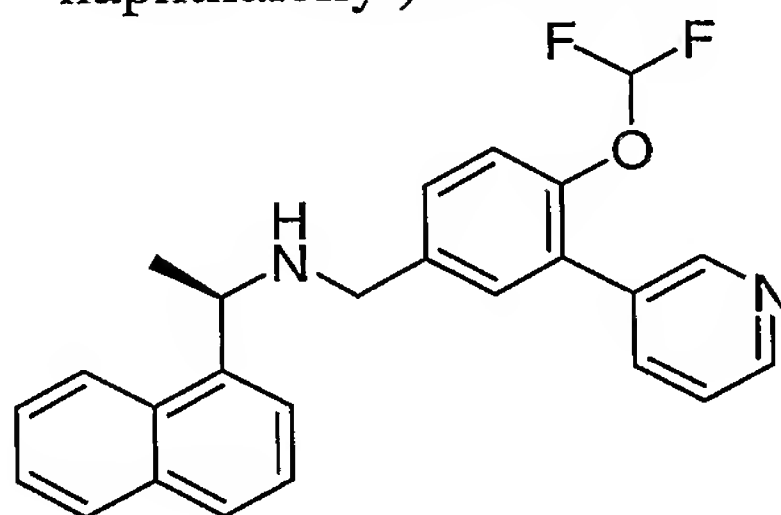
MW 384.424  
Mass found: 385, 251

15

**Example 407**

(1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

20



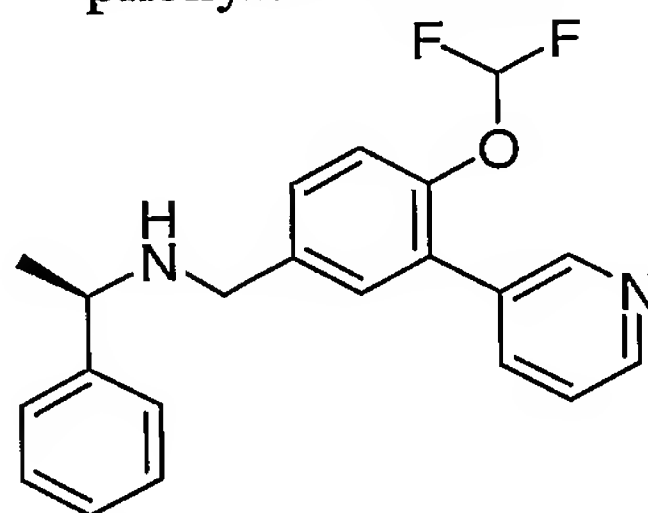
MW 404.458  
Mass found: 405, 155

25

**Example 408**

- 230 -

(1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine

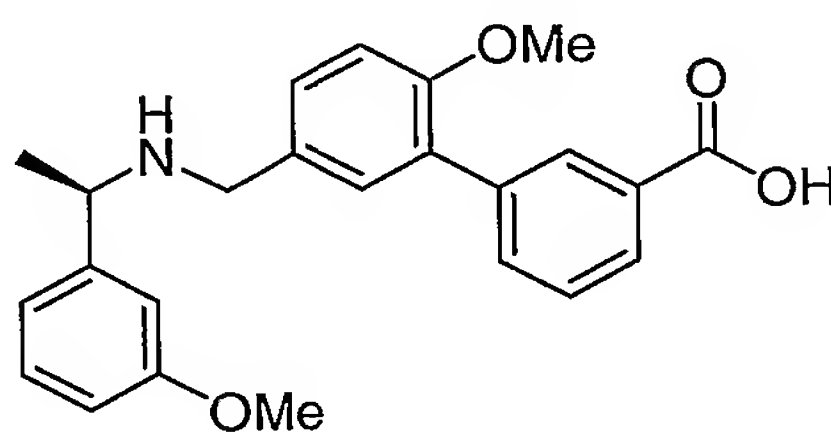


MW 354.398

Mass found: 355, 251

**Example 409**

2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid

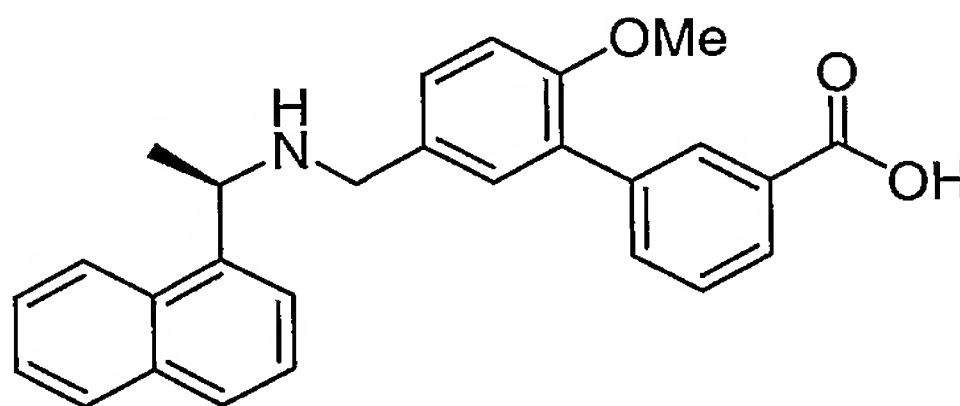


MW 391.465

Mass found: 241, 392

**Example 410**

2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid



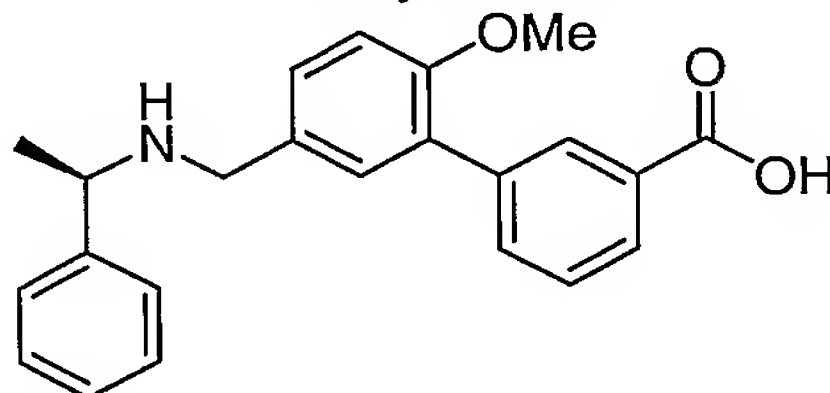
MW 411.499

Mass found: 155, 412, 241

**Example 411**

- 231 -

2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid



5

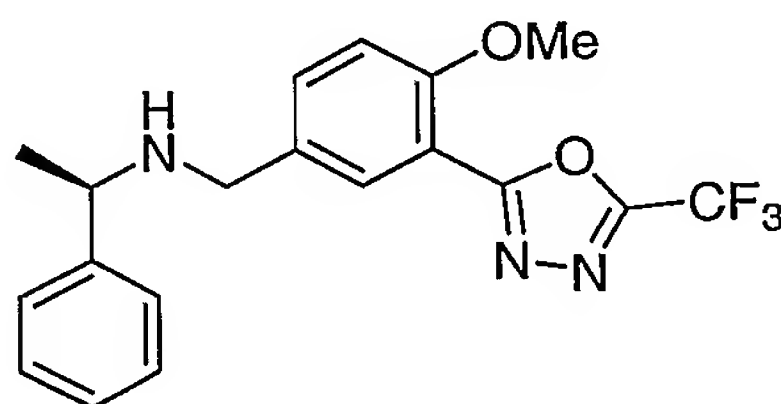
MW 361.439

Mass found: 241, 362

10

**Example 412**

(1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-phenylethanamine



15

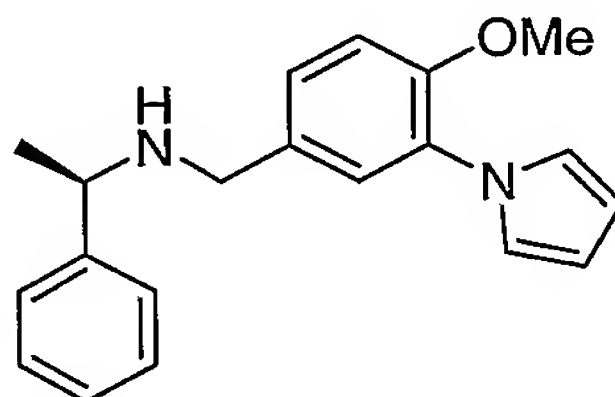
MW 377.364

Mass found: 274, 378

20

**Example 413**

(1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-phenylethanamine



25

MW 306.407

Mass found: 186, 307

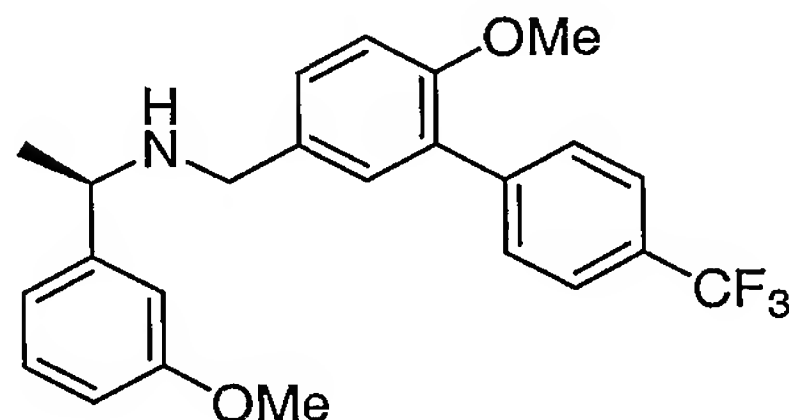
30

**Example 414**



- 232 -

(1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



5

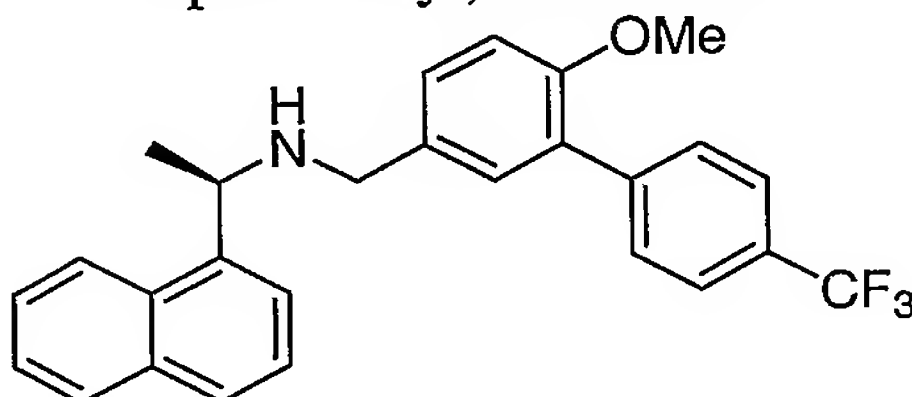
MW 415.453

Mass found: 265, 416

10

**Example 415**

(1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



15

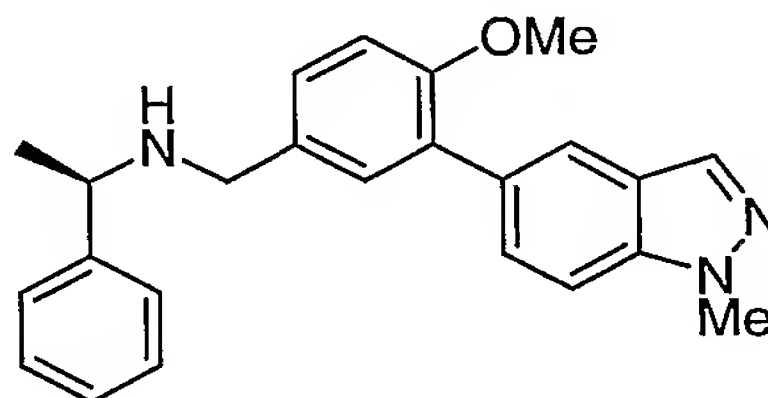
MW 435.487

Mass found: 155, 436

20

**Example 416**

(1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



25

MW 371.482

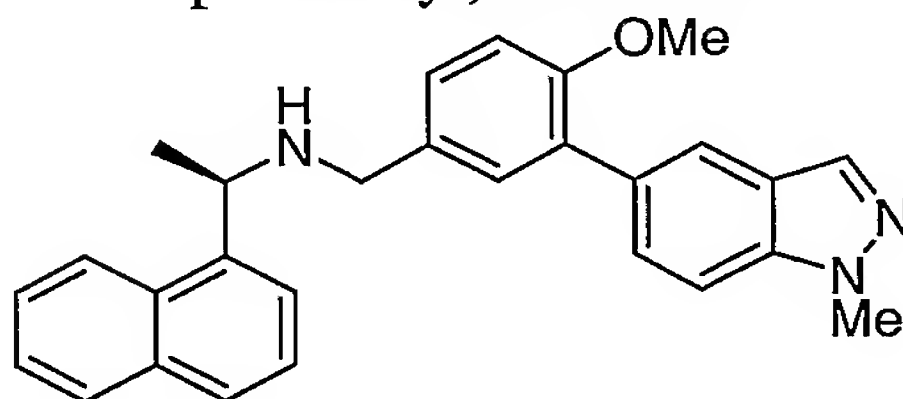
Mass found: 251, 372

30

**Example 417**

- 233 -

(1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



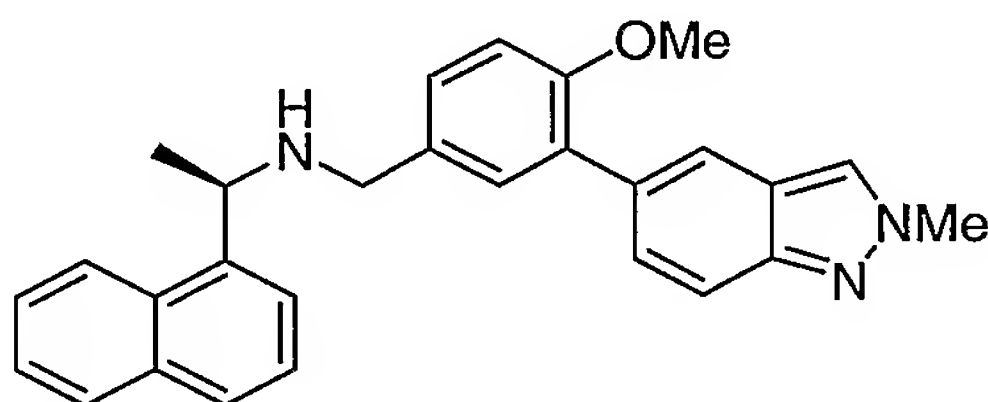
5

MW 421.541  
Mass found: 251, 422

**Example 418**

10

(1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



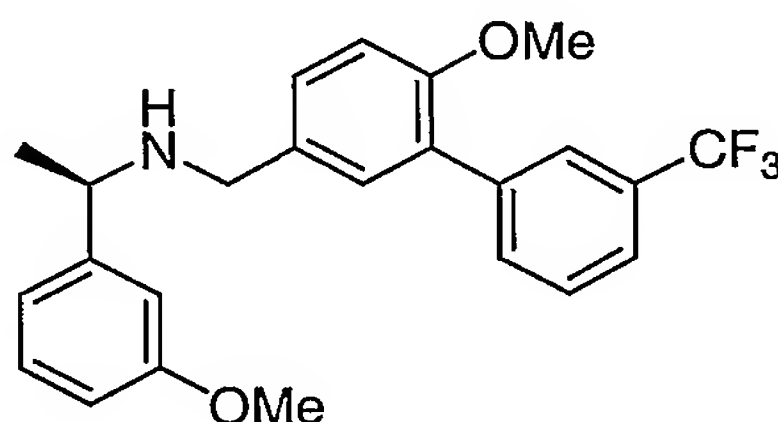
15

MW 421.541  
Mass found: 422, 251, 155

**Example 419**

20

(1R)-1-(3-(methoxy)phenyl)-N-((6-(methoxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



25

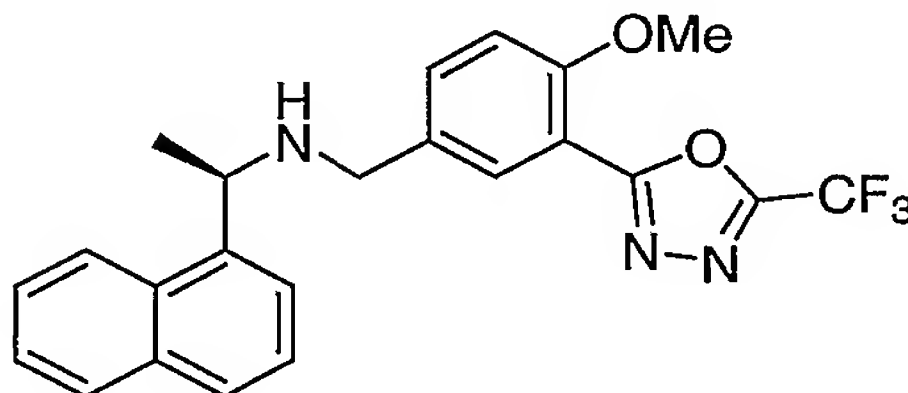
MW 415.453  
Mass found: 416, 265

30

**Example 420**

- 234 -

(1R)-N-((4-(methoxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



5

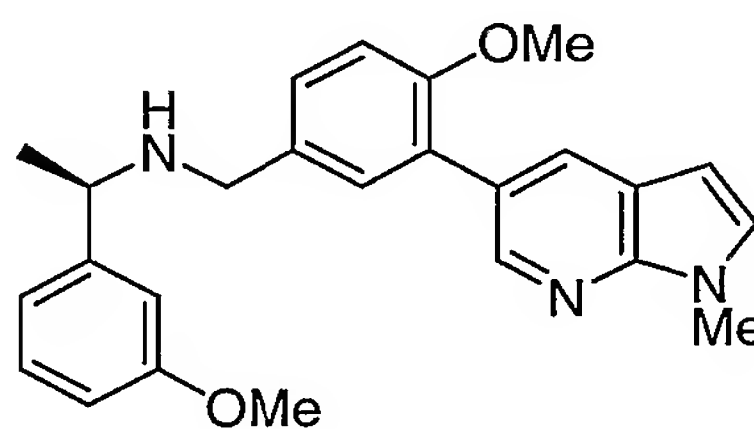
MW 427.424

Mass found: 155, 428

10

**Example 421**

(1R)-N-((4-(methoxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



15

MW 401.507

Mass found: 251, 402, 268

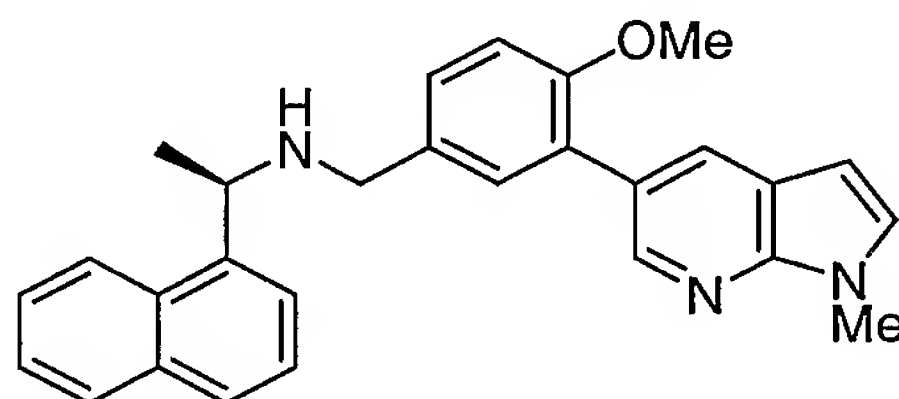
20

- 235 -

**Example 422**

(1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

5



MW 421.541

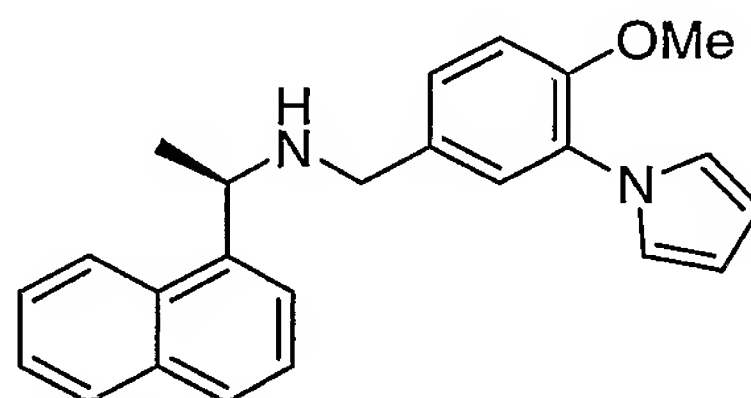
Mass found: 422, 251, 155, 268

10

**Example 423**

(1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 356.467

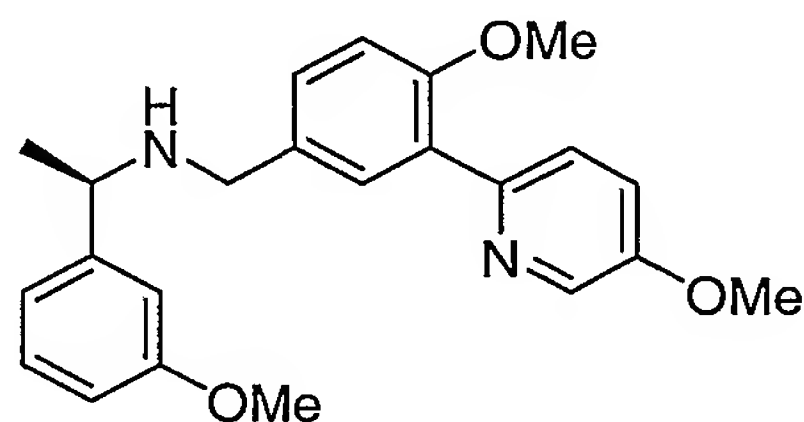
Mass found: 155, 357

20

**Example 424**

(1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

25



MW 378.469

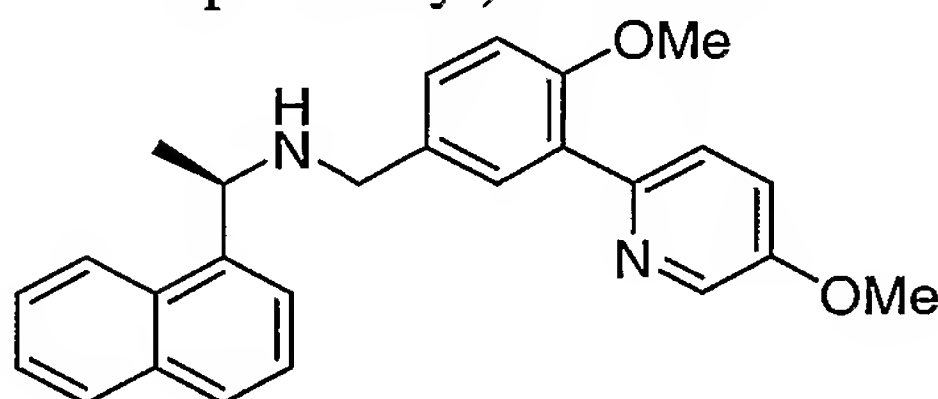
Mass found: 379, 757

30

- 236 -

**Example 425**

(1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

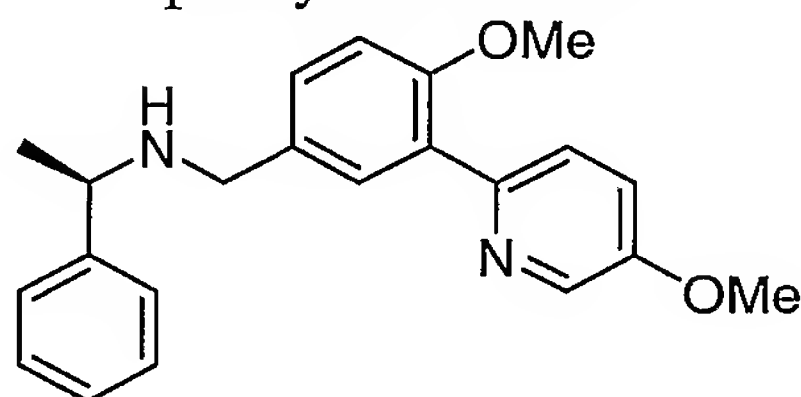


MW 398.503

Mass found: 399, 797

**Example 426**

(1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine

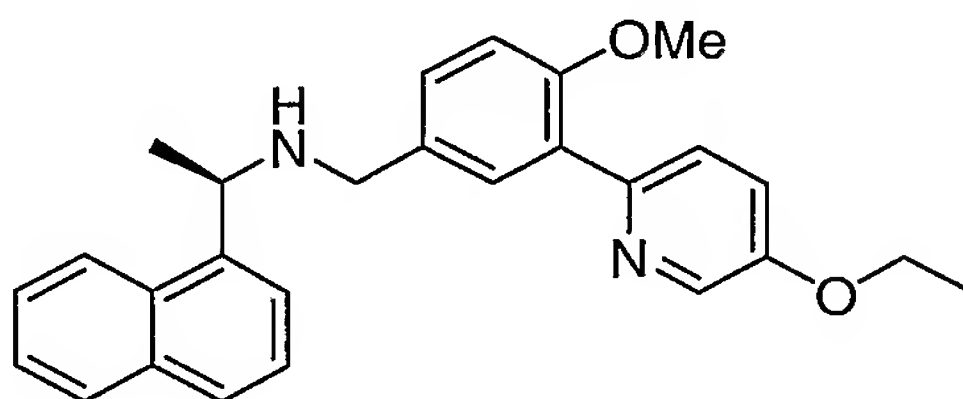


MW 348.444

Mass found: 349, 697

**Example 427**

(1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



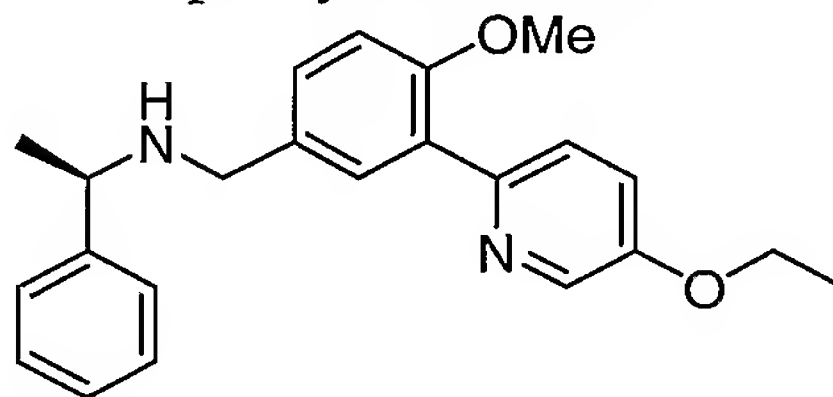
MW 412.53

Mass found: 413, 155, 242, 259

**Example 428**

- 237 -

(1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethylamine



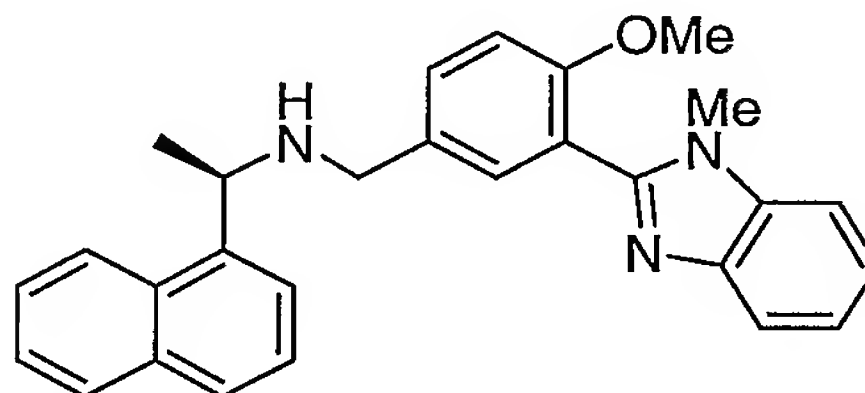
5

MW 362.47  
Mass found: 242, 363, 725

**Example 429**

10

(1R)-N-((3-(1-methyl-1H-benzimidazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



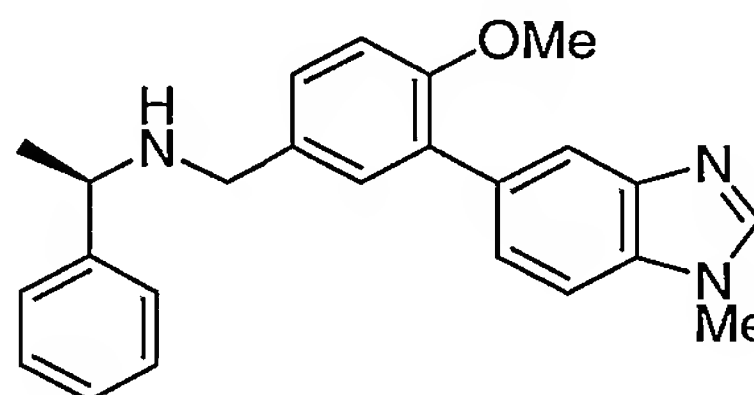
15

MW 421.541  
Mass found: 422, 155

**Example 430**

20

(1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethylamine



25

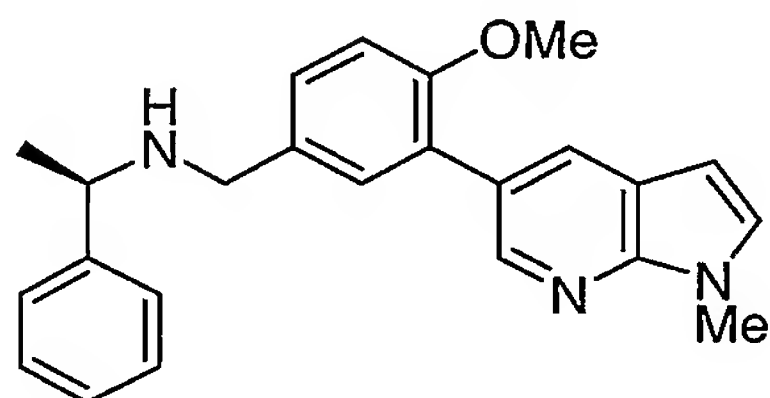
MW 371.482  
Mass found: 251, 268, 372, 743

30

**Example 431**

- 238 -

(1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-phenylethanamine



5

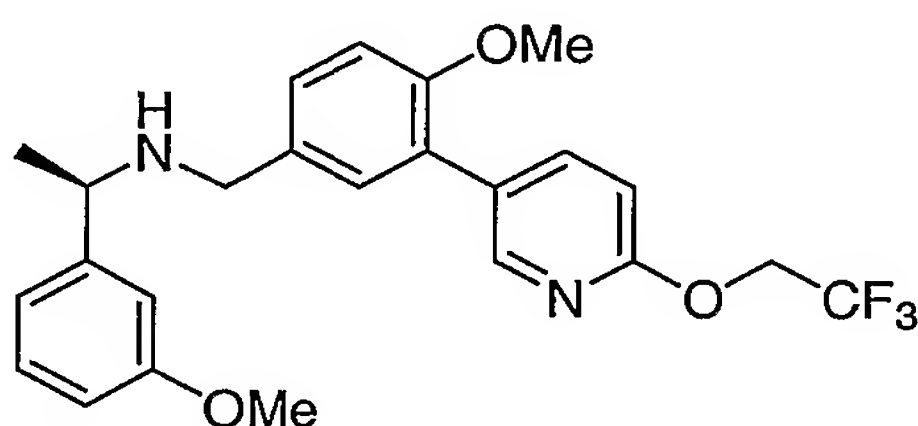
MW 371.482

Mass found: 251, 372, 268

10

**Example 432**

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine



15

MW 446.466

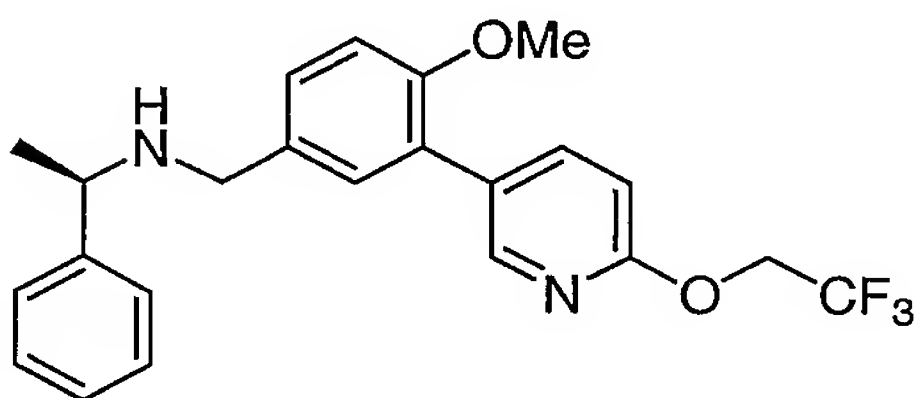
Mass found: 447, 296

20

**Example 433**

(1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

25



MW 416.441

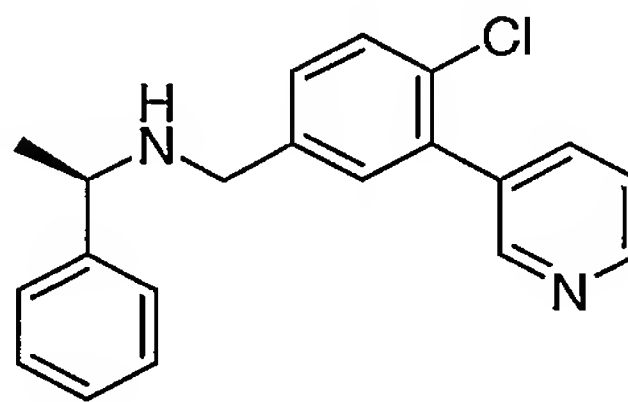
Mass found: 417, 296

30

**Example 434**

- 239 -

(1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine

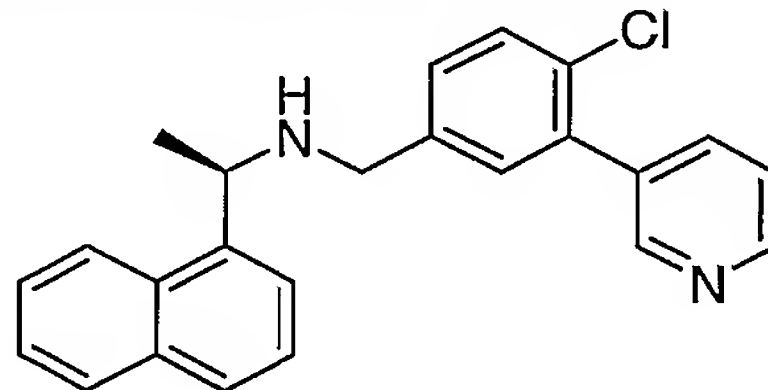


5

MW 322.837  
Mass found: 323, 219, 645**Example 435**

10

(1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

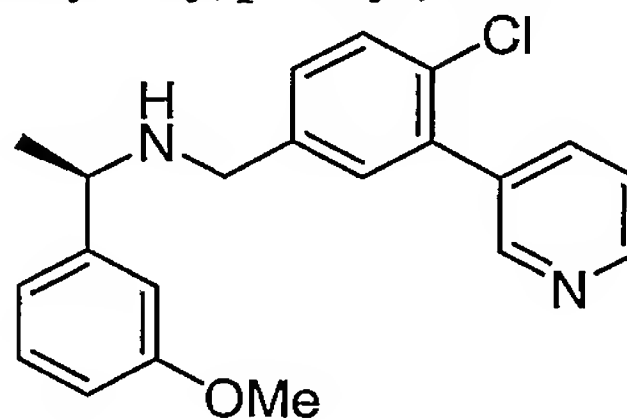


15

MW 372.897  
Mass found: 155, 373, 219**Example 436**

20

(1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



25

MW 352.863  
Mass found: 353, 219

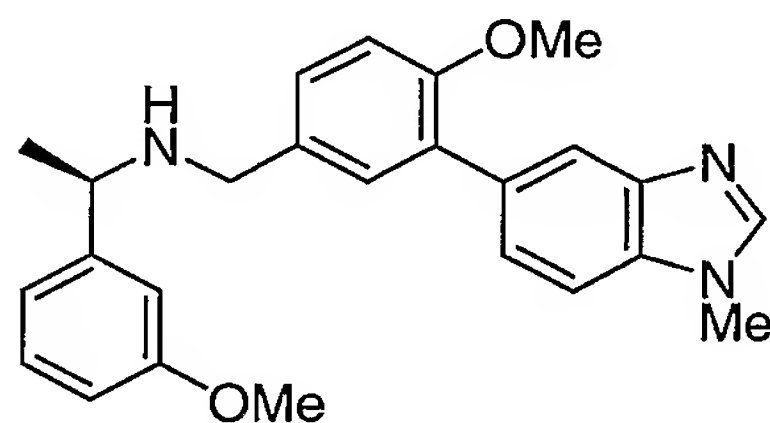


- 240 -

**Example 437**

(1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

5



MW 401.507

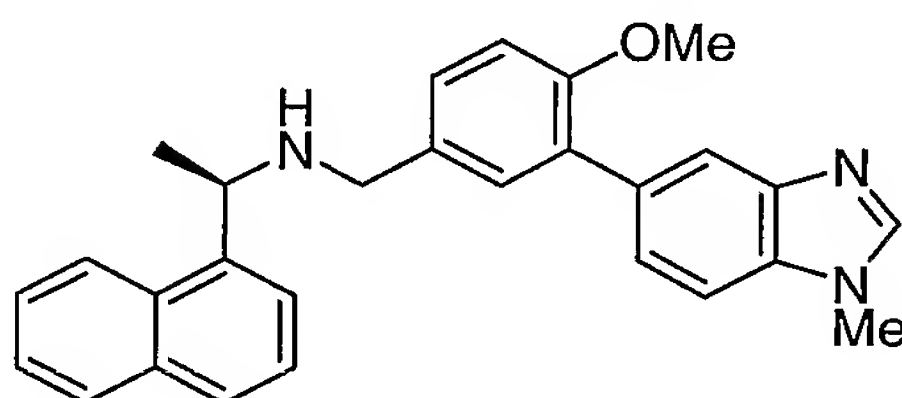
Mass found: 402, 251, 268

10

**Example 438**

(1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 421.541

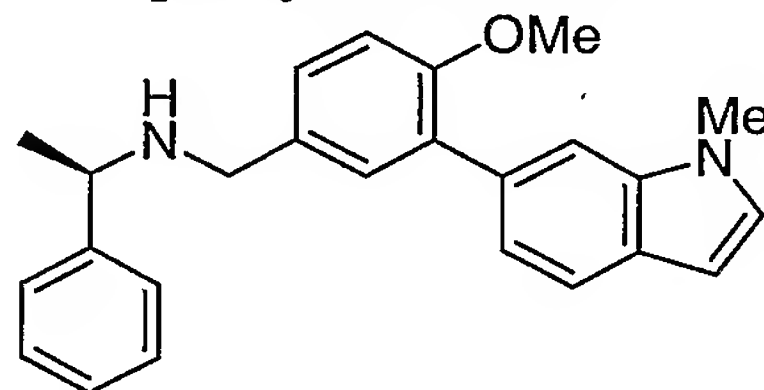
Mass found: 155, 422, 251, 268

20

**Example 439**

(1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

25



MW 370.493

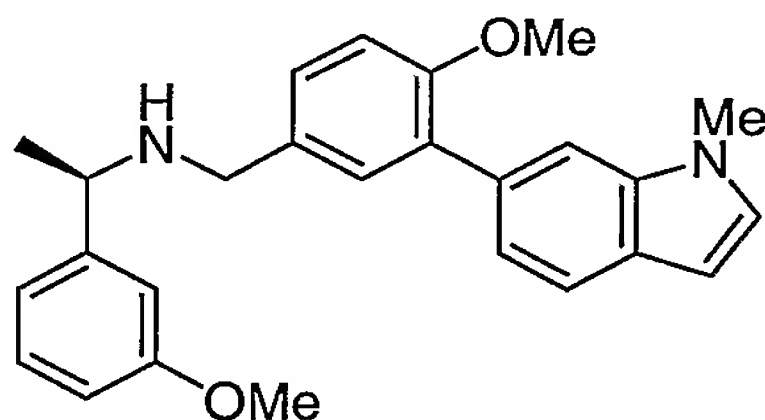
Mass found: 250, 371

30

**Example 440**

- 241 -

(1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methoxy)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



5

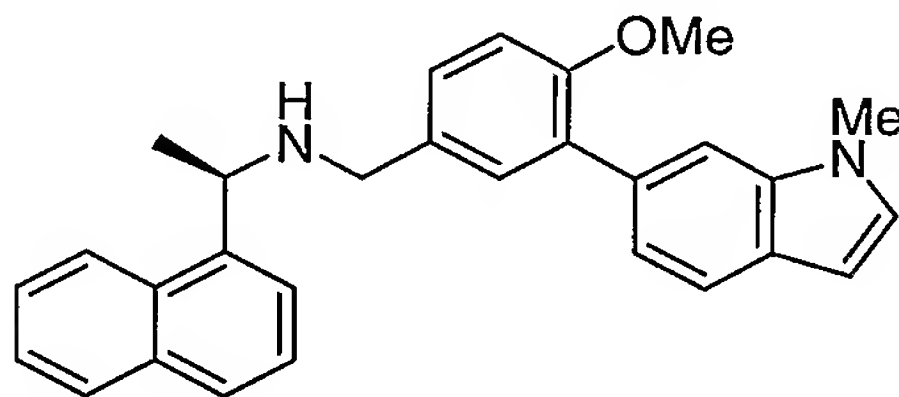
MW 400.519  
Mass found: 401, 250

10

**Example 441**

(1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



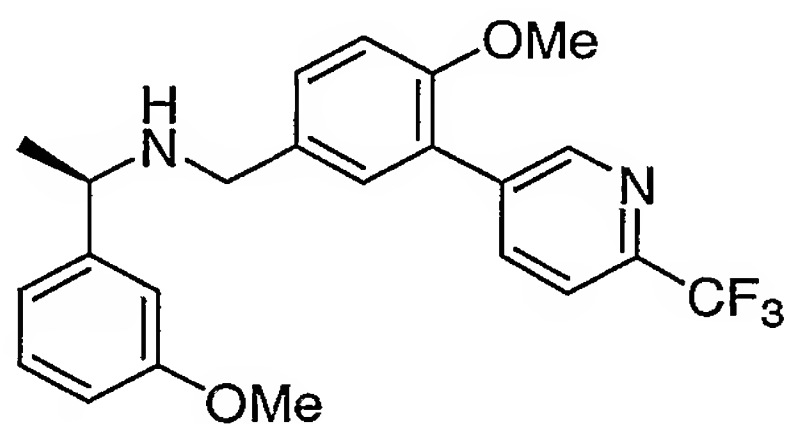
MW 420.553  
Mass found: 421, 250

20

**Example 442**

(1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine

25



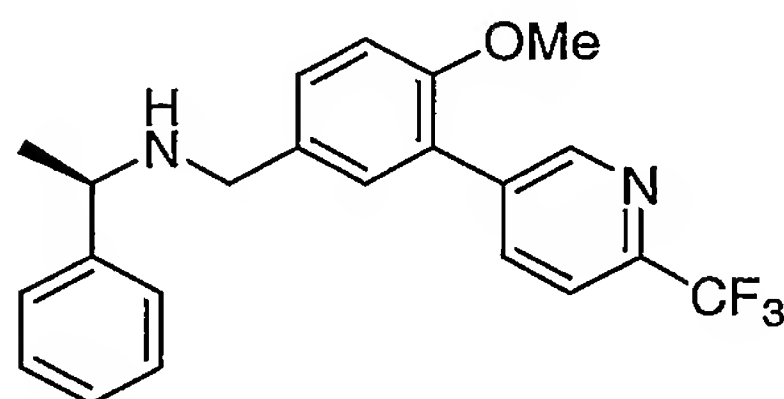
MW 416.441  
Mass found: 417, 947

30

**Example 443**

- 242 -

(1R)-N-((4-(methoxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine



5

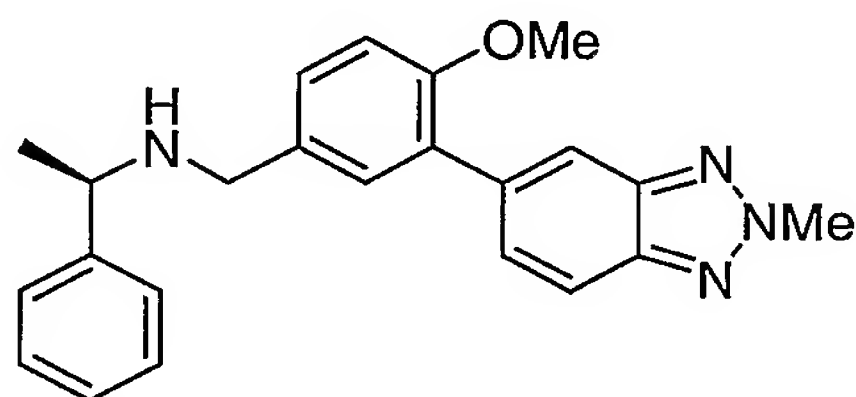
MW 386.415  
Mass found: 887, 387, 428

10

**Example 444**

(1R)-N-((3-(2-ethyl-2H-1,2,3-benzotriazol-5-yl)-4-(methoxy)phenyl)methyl)-1-phenylethanamine

15



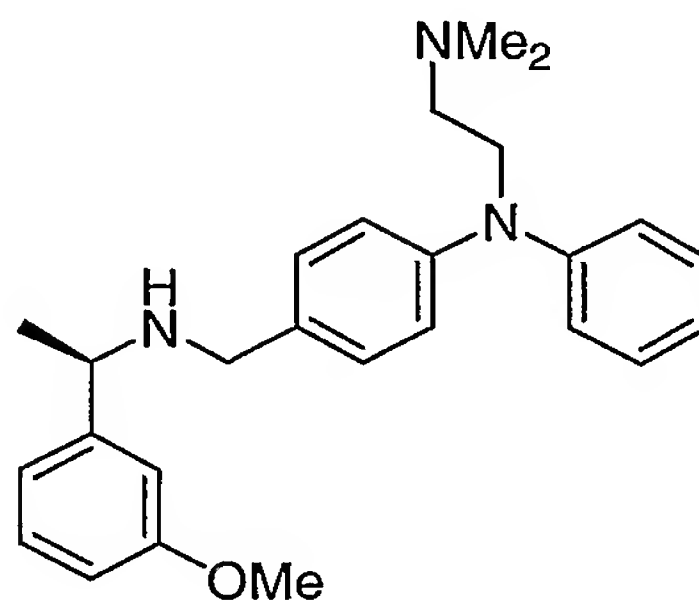
MW 386.496  
Mass found: 887, 387

20

**Example 445**

N-1,N-1-dimethyl-N-2-(4-(((1R)-1-(3-(methoxy)phenyl)ethyl)amino)methyl)phenyl)-N-2-phenyl-1,2-ethanediamine

25



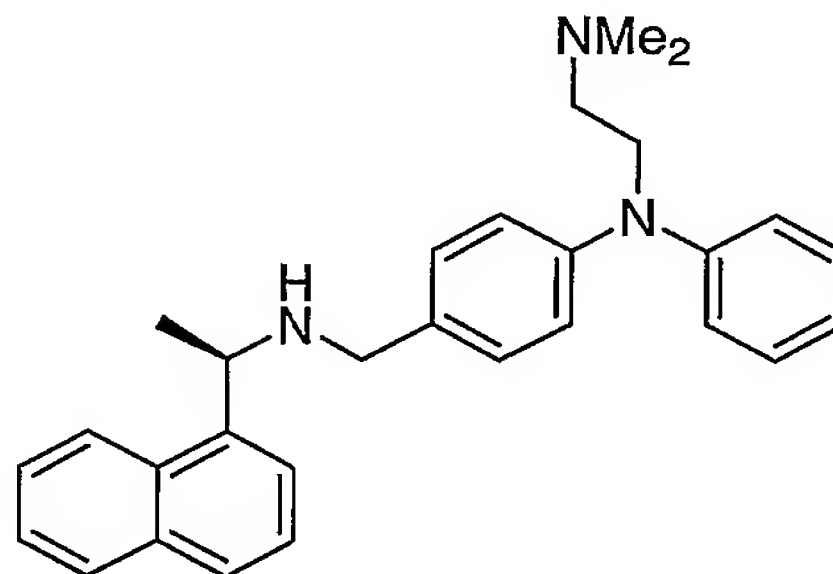
MW 403.567  
Mass found: 253, 404

30

- 243 -

**Example 446**

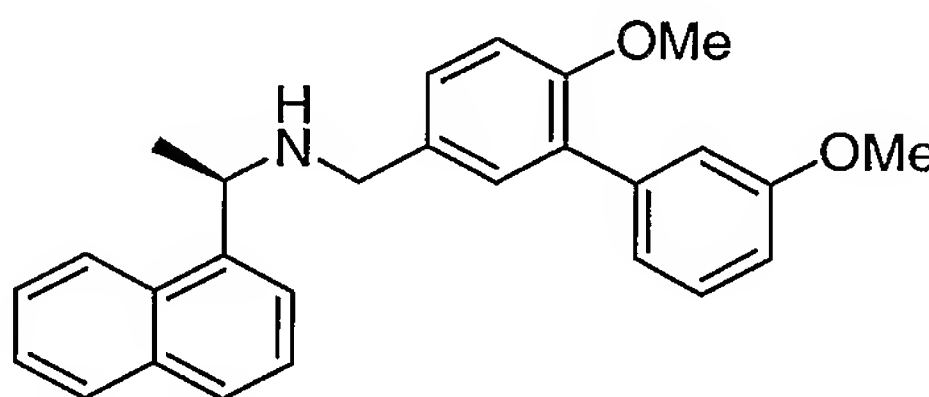
5     N-1,N-1-dimethyl-N-2-(4-(((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-  
N-2-phenyl-1,2-ethanediamine



10                    MW 423.601  
Mass found: 253, 424

**Example 447**

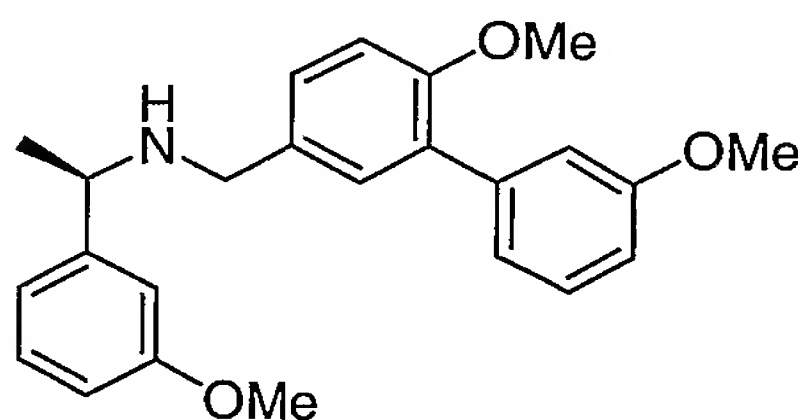
15     (1R)-N-((3',6-bis(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-  
naphthalenyl)ethanamine



20                    MW 397.515  
Mass found: 398

**Example 448**

25     (1R)-N-((3',6-bis(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-  
(methoxy)phenyl)ethanamine



30

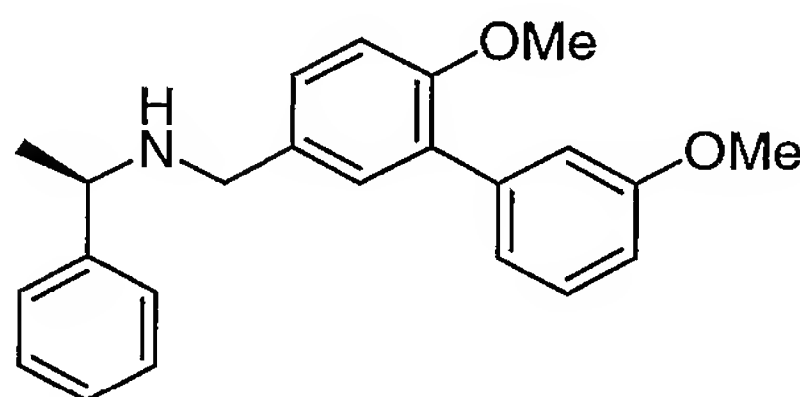
- 244 -

MW 377.481  
Mass found: 378

5

**Example 449**

(1R)-N-((3',6-bis(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



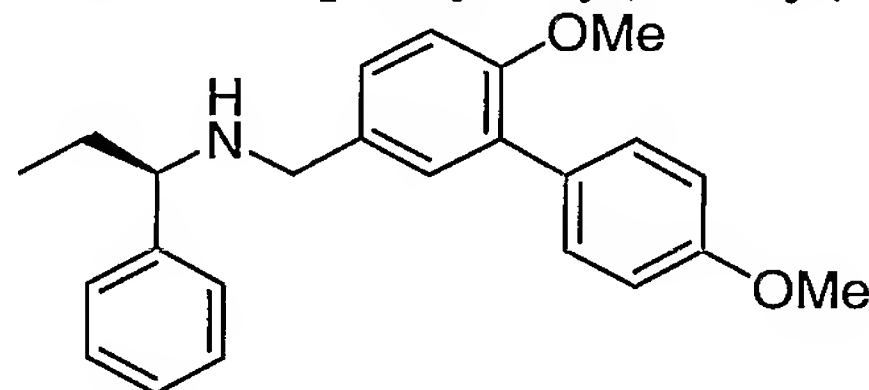
10

MW 347.456  
Mass found: 348

15

**Example 450**

(1R)-N-((4',6-bis(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenyl-1-propanamine



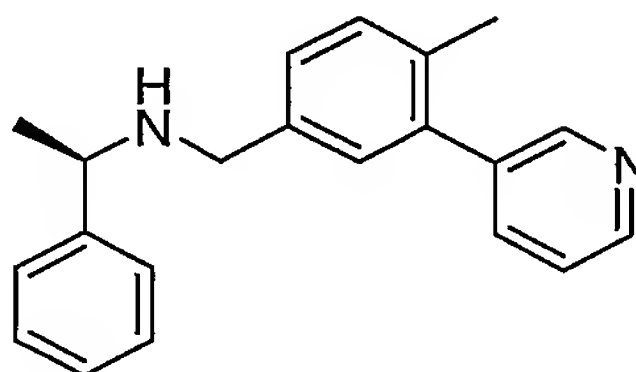
20

MW 361.482  
Mass found: MS(EI) calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub> 362 (MH<sup>+</sup>), Found: 362, 227, 212

25

**Example 451**

(1R)-N-((4-methyl-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine



30

MW 302.419  
Mass found: MS(EI) calcd for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub> 303 (MH<sup>+</sup>) Found: 303, 199, 183

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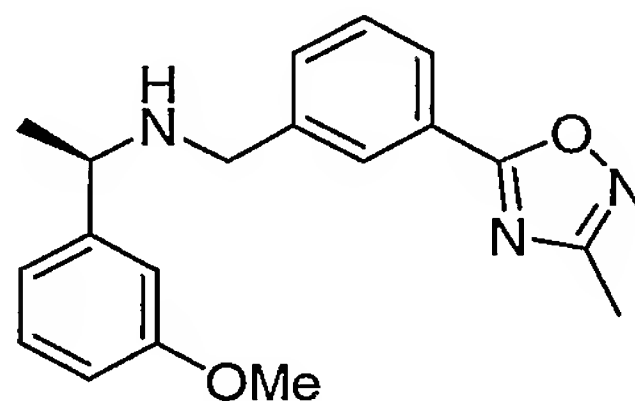
Examples 452-465 were prepared using Method A:

5

**Example 452**

(1R)-N-((3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



MW 323.394

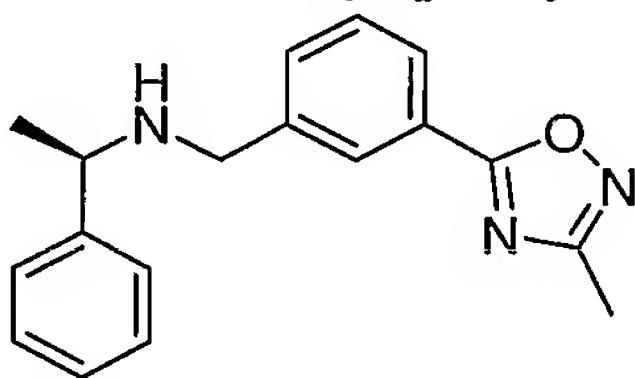
Mass found: 324, 231, 190

15

**Example 453**

(1R)-N-((3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methyl)-1-phenylethanamine

20



MW 293.368

Mass found: 294, 231, 190

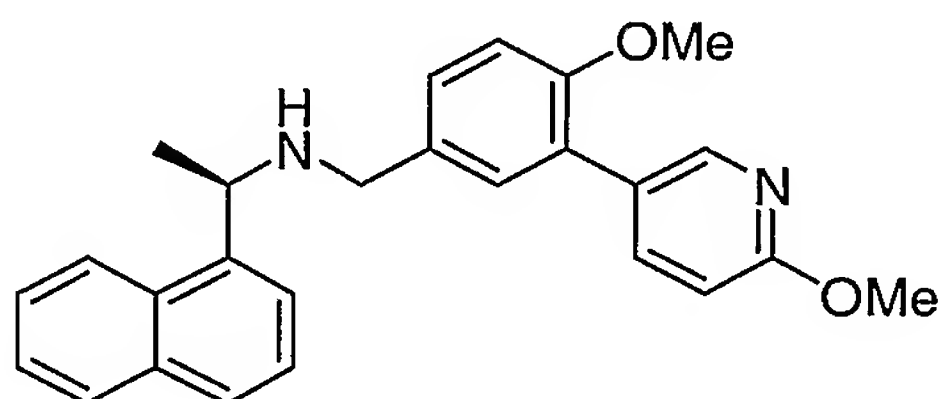
25

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**Example 454**

(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

5



MW 398.503

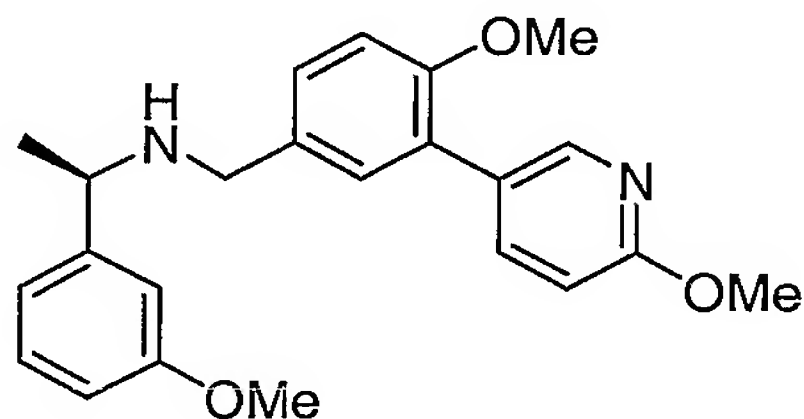
Mass found: 399, 155, 245, 228

10

**Example 455**

(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

15



MW 378.469

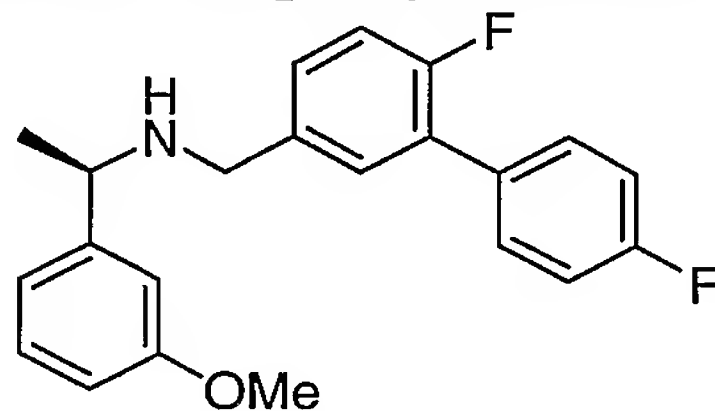
Mass found: 379

20

**Example 456**

(1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

25



MW 353.41

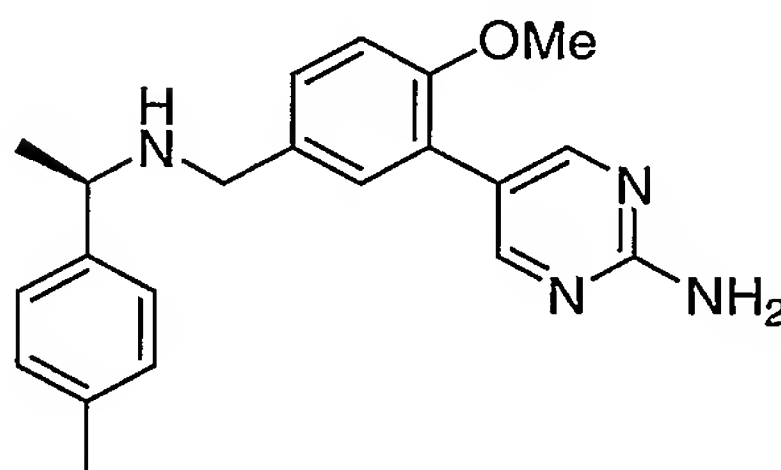
Mass found: 354

30

**Example 457**

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5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-pyrimidinamine



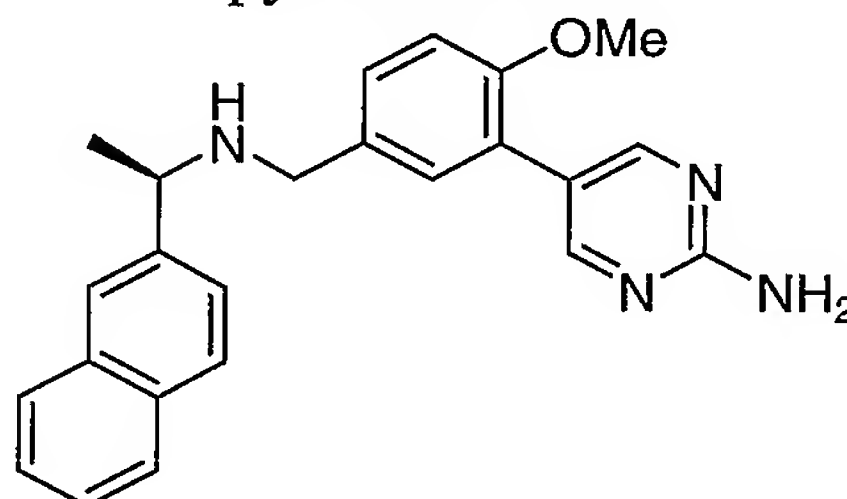
5

MW 348.448  
Mass found: 214, 349, 231

10

**Example 458**

5-(2-(methyloxy)-5-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyrimidinamine



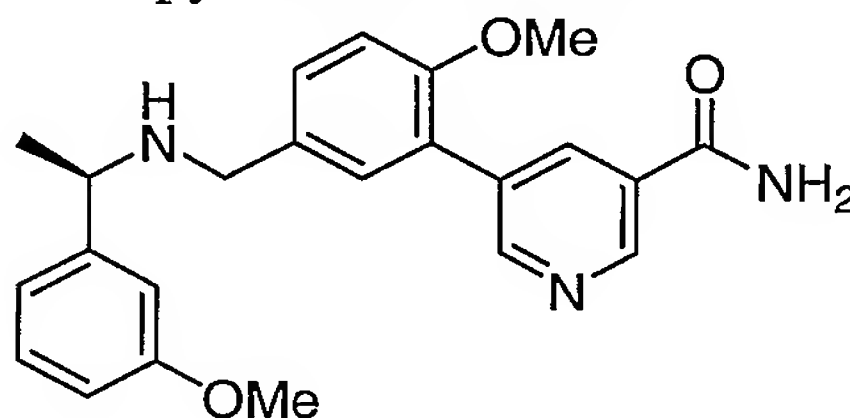
15

MW 384.481  
Mass found: 155, 385, 231

20

**Example 459**

5-(3-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



25

MW 361.443  
Mass found: 362, 228

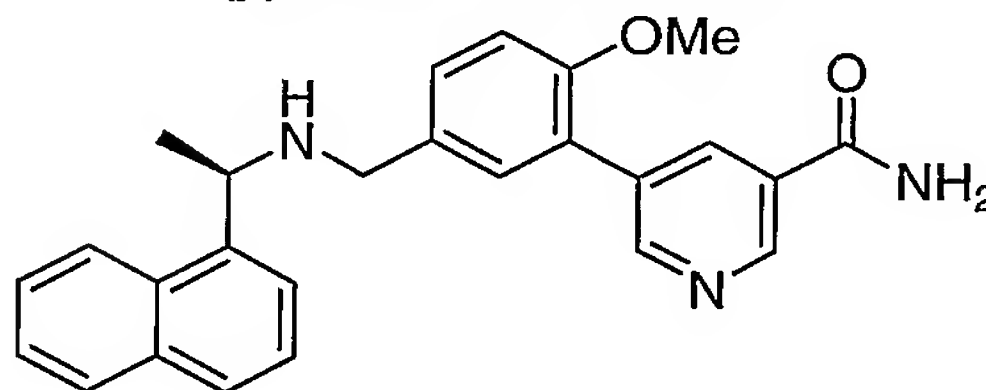
30



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**Example 460**

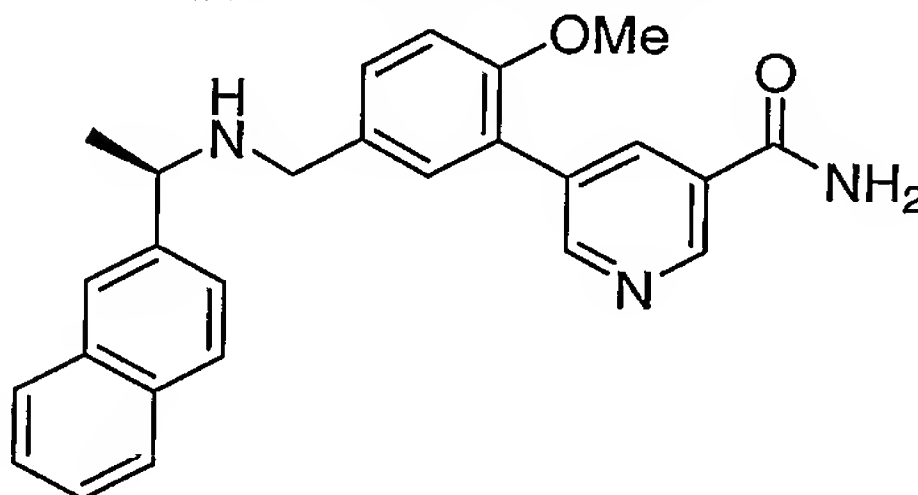
5 5-(3-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



MW 381.477  
Mass found: 155, 382, 228

**Example 461**

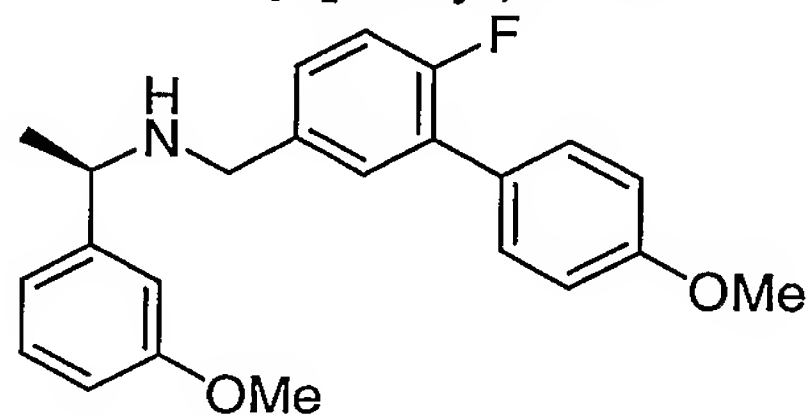
15 5-(3-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



MW 381.477  
Mass found: 155, 382, 228

**Example 462**

25 (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



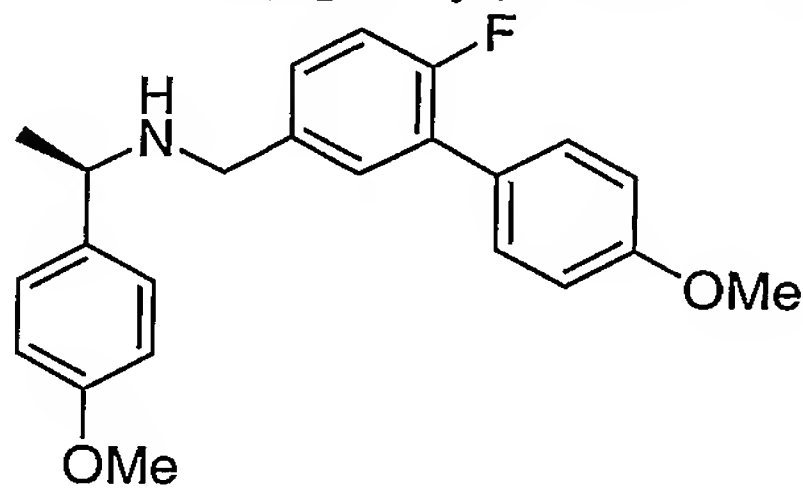
MW 365.446  
Mass found: 366, 215

30

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**Example 463**

(1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

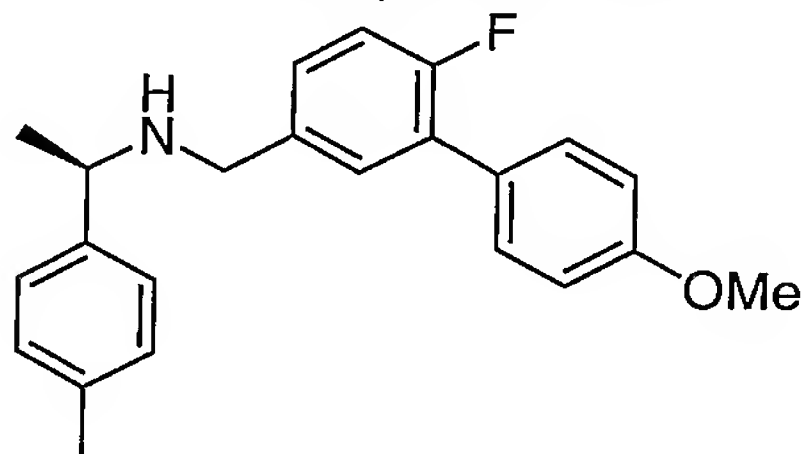


MW 365.446

Mass found: 366, 215

**Example 464**

(1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



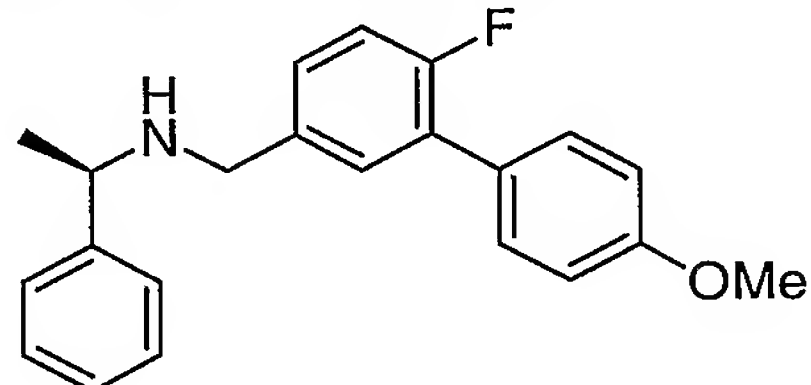
MW 349.447

Mass found: 350, 215

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**Example 465**

(1R)-N-((6-fluoro-4'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



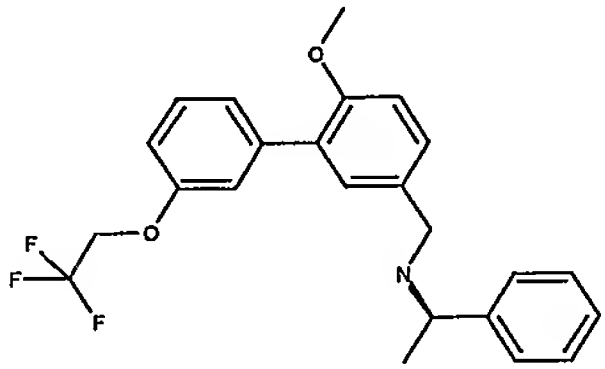
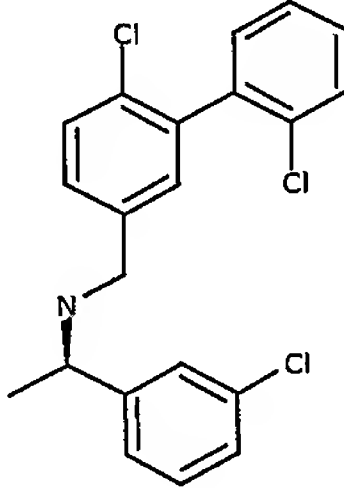
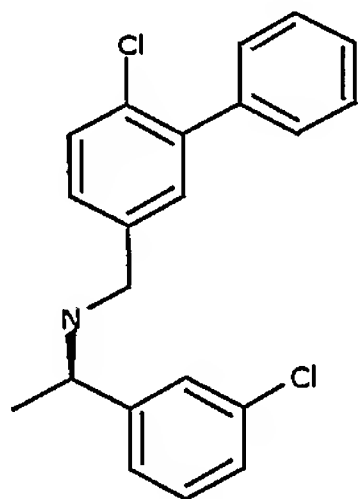
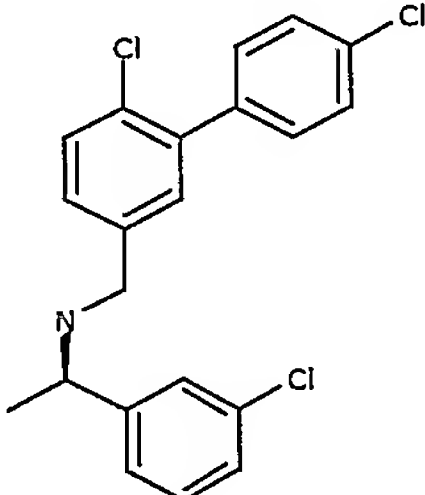
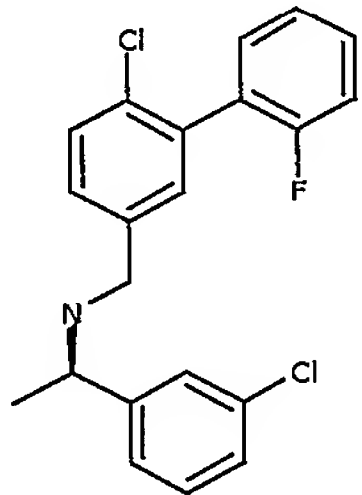
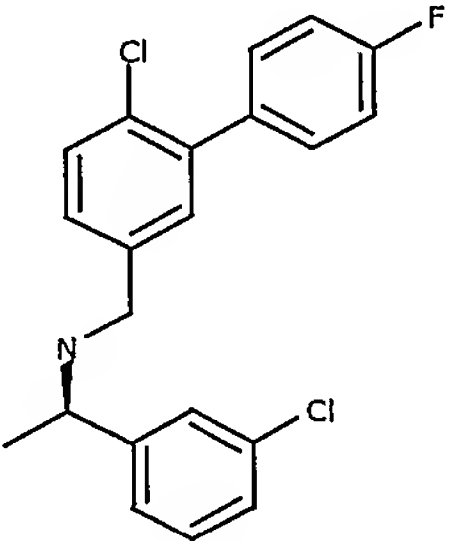
MW 335.42

Mass found: 336, 215

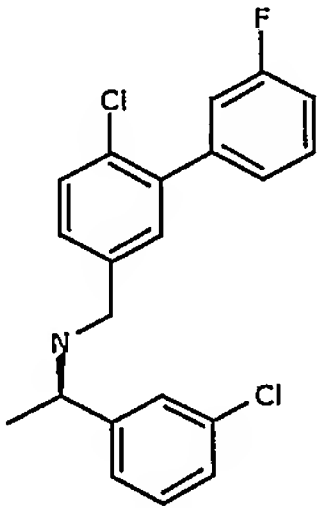
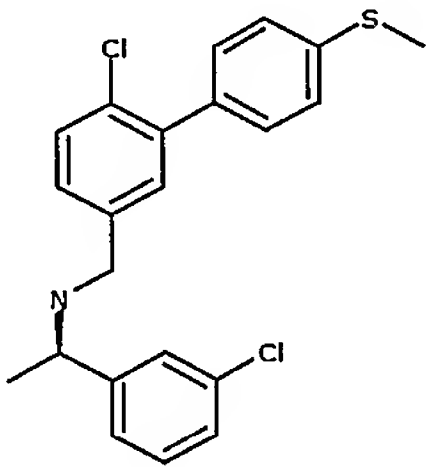
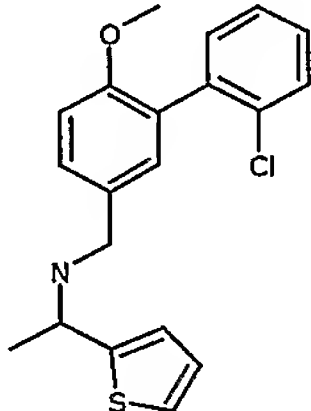
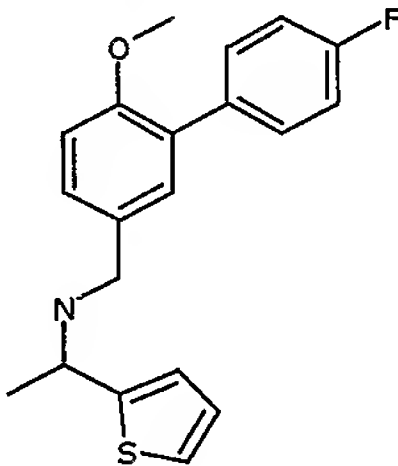
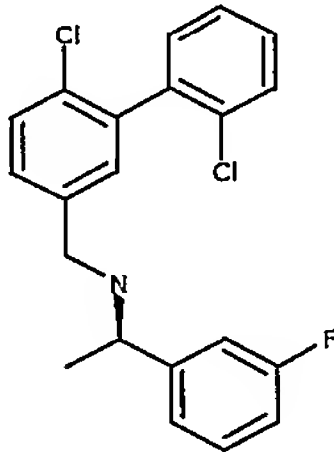
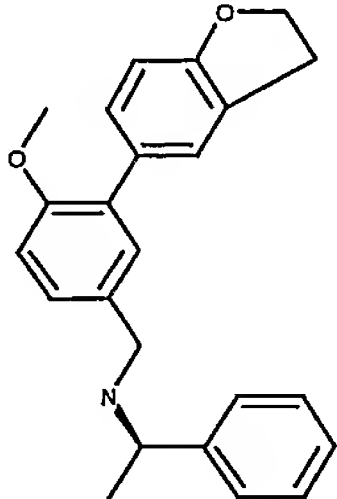
The following compounds were prepared using Synthetic Method C:

Example No:	Structure
466	
467	
468	
469	

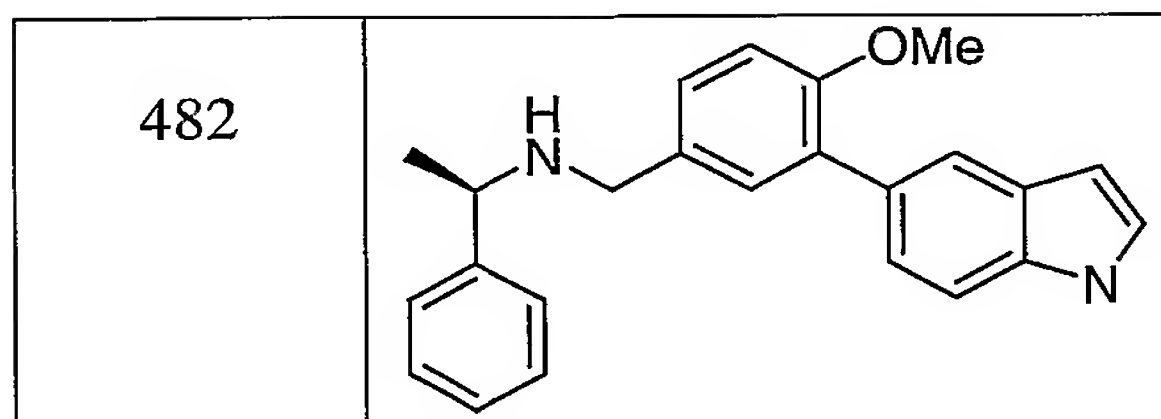
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470	
471	
472	
473	
474	
475	

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476	
477	
478	
479	
480	
481	

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### Biological Activity

The activities of the compounds of the present invention on calcium  
5 receptors were measured. In one embodiment, the measurement was performed in  
accordance with the method described in Example 4 of Nemeth et al.,  
PCT/US95/13704 (International Publication No. WO96/12697) herein  
incorporated by reference.

A 4.0-kb *NotI*-*HindIII* fragment of the human parathyroid cell  $\text{Ca}^{2+}$   
10 receptor (hPCaR) cDNA was subcloned into the mammalian expression vector  
pCEP4 (Invitrogen) containing the hygromycin-resistant gene as a selectable  
marker. This plasmid was transfected into HEK 293 cells by calcium phosphate  
precipitation. Transfected cells were grown in Dulbecco's modified Eagle's  
medium containing 10% fetal bovine serum and hygromycin (200  $\mu\text{g/mL}$ ).  
15 Hygromycin-resistant colonies were subcloned and assayed for hPCaR mRNA by  
solution hybridization using a  $^{32}\text{P}$ -labeled RNA probe complementary to the (4.0  
kb) hPCaR sequence (Garrett, et al., J. Biol. Chem. 270, 12919-12925 (1995)).  
Clone 7 was used to assess the effects of compounds on  $[\text{Ca}^{2+}]_i$ . This stably  
transfected cell line is termed HEK 293 4.0-7. For measurements of  $[\text{Ca}^{2+}]_i$ , the  
20 cells were recovered from tissue culture flasks by brief treatment with 0.02%  
EDTA and then washed and resuspended in PCB containing 1mM  $\text{CaCl}_2$  and  
0.1% Bovine Serum Albumin ("BSA"). The cells were loaded with fluo-3 by  
incubation for 30 min at 37 °C, with parathyroid cell buffer (126mM NaCl, 4mM  
KCl, 1mM  $\text{MgSO}_4$ , 0.7mM  $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$ , 20mM HEPES·NaOH (pH 7.45))  
25 containing 0.5% BSA in 1mM  $\text{CaCl}_2$  and 2 $\mu\text{M}$  fluo-3 acetoxymethyl ester. The  
cells were subsequently washed, each test compound was added to the cells and  
the fluorescence was recorded by using excitation and emission wavelengths of  
485 and 530 nm, respectively.

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The following compounds of the invention were tested according to the procedure described above and found to have an EC<sub>50</sub> of 10  $\mu$ M or less:

- (1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethamine;
- 5 (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethamine;
- (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-(1-  
10 naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-(ethyloxy)-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethamine;
- 15 (1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-  
20 (1-naphthalenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(4-  
25 methylphenyl)ethanamine;
- (1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-phenylethamine;
- (1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-methylphenyl)ethanamine;
- 30 (1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;

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- (1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- 5 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- 2'-(methyloxy)-5'-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- 2'-(methyloxy)-5'-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-
- 10 biphenyl-3-carbonitrile;
- 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- (1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)ethanamine;
- (1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-
- 20 methylphenyl)ethanamine;
- (1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 25 (1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-
- 30 (methyloxy)phenyl)ethanamine;
- (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;



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- 5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-  
2-furancarboxylic acid;  
4-oxo-4-((5-(3-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-  
pyridinyl)amino)butanoic acid;  
5 4-((5-(3-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-  
pyridinyl)amino)-4-oxobutanoic acid;  
(1R)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(1-  
naphthalenyl)ethanamine;  
(1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(4-  
10 (methyloxy)phenyl)ethanamine;  
(1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-  
(methyloxy)phenyl)ethanamine;  
(1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(2-  
naphthalenyl)ethanamine;  
15 (1R)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-phenylethanamine;  
(1R)-1-(4-(methyloxy)phenyl)-N-((3-(6-(methyloxy)-3-  
pyridazinyl)phenyl)methyl)ethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((3-(6-(methyloxy)-3-  
pyridazinyl)phenyl)methyl)ethanamine;  
20 (1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(2-  
naphthalenyl)ethanamine;  
(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-  
naphthalenyl)ethanamine;  
(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-  
25 (methyloxy)phenyl)ethanamine;  
(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-  
(methyloxy)phenyl)ethanamine;  
(1R)-1-phenyl-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine;  
(1R)-1-(4-(methyloxy)phenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine;  
30 (1R)-1-(3-(methyloxy)phenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine;  
(1R)-1-(2-naphthalenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;  
(1R)-1-phenyl-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;

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- (1R)-1-(1-naphthalenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;  
(1R)-1-(4-methylphenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;  
(1R)-1-(4-(methyloxy)phenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;  
5 (1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;  
(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-1-(4-methylphenyl)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)ethanamine;  
(1R)-1-(4-(methyloxy)phenyl)-N-((3-(6-methyl-3-  
10 yridinyl)phenyl)methyl)ethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((3-(6-methyl-3-  
yridinyl)phenyl)methyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(2-  
naphthalenyl)ethanamine;  
15 (1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(1-  
naphthalenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(4-  
methylphenyl)ethanamine;  
20 (1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-  
thienyl)phenyl)methyl)ethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-  
thienyl)phenyl)methyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)-1-phenylethanamine;  
25 (1R)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)-1-(4-  
methylphenyl)ethanamine;  
(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-  
pyrimidinyl)phenyl)methyl)ethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-  
30 pyrimidinyl)phenyl)methyl)ethanamine;  
(1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
N-(3'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide;

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- N-(3'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide;
- N-(3'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide;
- 5 (1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;
- 10 (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(4-methylphenyl)ethanamine;
- 15 (1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;
- 20 (1R)-N-((3',4'-dimethyl-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- 25 (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- 30 (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-1-(1-naphthalenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;

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- (1R)-1-phenyl-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;  
(1R)-1-phenyl-N-((4-(1-pyrrolidinyl)phenyl)methyl)ethanamine;  
(1R)-N-((4-(3,5-dimethyl-4-isoxazolyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;  
(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;  
(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine;
- 10 (1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-phenylethanamine;  
5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;  
(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(3-
- 15 (methyloxy)phenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-phenylethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;  
5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;  
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-
- 25 pyrazinyl)phenyl)methyl)ethanamine;  
(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-phenylethanamine;

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- 5-(2-(methyloxy)-5-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
- (1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;
- 5 (1R)-1-(4-methylphenyl)-N-((3-(9-methyl-9H-purin-6-yl)phenyl)methyl)ethanamine;
- (1R)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 N-(5-(3-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide;
- N-(5-(3-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide;
- 15 N-(5-(3-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide;
- (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-N-((2',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 20 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 N-(4'-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide;
- N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea;
- 30 N-(4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide;

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- (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea;
- 5 (1R)-N-((4-(methyloxy)-3-(2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea;
- (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 10 N-(4'-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide;
- (1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-phenylethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 25 3-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-N-(3-(4-morpholinyl)propyl)-2-pyridinamine;
- (1R)-N-((4-(methyloxy)-3-(6-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 30 3-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-N-(tetrahydro-2-furanylmethyl)-2-pyridinamine;
- 5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine;



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- N,N-dimethyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine;
- (1R)-N-((4-(methyloxy)-3-(4-piperidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 2-(5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide;
- 2-(5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide;
- 2-(5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide;
- 10 (1R)-N-((4-(methyloxy)-3-(2-(4-morpholinyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2-fluoro-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 15 (1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1,3-thiazol-2-amine;
- (1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 30 N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-N-((1R)-1-(3-(methyloxy)phenyl)ethyl)amine;

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- N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methoxy)phenyl)methyl)-N-((1R)-1-(1-naphthalenyl)ethyl)amine;  
 (1R)-N-((4-(methoxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 5 (1R)-N-((4-(methoxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-N-((4-(methoxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-phenylethanamine;  
 (1R)-N-((4-(methoxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;  
 10 (1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methoxy)phenyl)methyl)-1-phenylethanamine;  
 2'-(methoxy)-5'-((((1R)-1-(3-(methoxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;  
 (1R)-N-((4-(methoxy)-3-(1-methyl-4-piperidinyl)phenyl)methyl)-1-(3-  
 15 (methoxy)phenyl)ethanamine;  
 2'-(methoxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;  
 (1R)-N-((4-(methoxy)-3-(1-methyl-4-piperidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 20 ethyl 2'-(methoxy)-5'-((((1R)-1-(3-(methoxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;  
 ethyl 2'-(methoxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;  
 ethyl 2'-(methoxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-  
 25 carboxylate;  
 ethyl 4-(2-(methoxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-1-piperidinecarboxylate;  
 ethyl 4-(2-(methoxy)-5-((((1R)-1-(3-(methoxy)phenyl)ethyl)amino)methyl)phenyl)-1-piperidinecarboxylate;  
 30 ethyl 4-(2-(methoxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1-piperidinecarboxylate;



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- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 5 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- 1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- 1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- 10 (1R)-N-((6-(methyloxy)-4'-(methanesulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 15 N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-methylphenyl)ethanamine;
- 3-(1-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)amino)ethyl)benzonitrile;
- (1R)-1-(3-((2-(methyloxy)ethyl)oxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 20 (1R)-N-((6-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- 30 (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;

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- (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)ethanamine;
- 15 (1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)ethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 25 (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-(1-piperidinyl)-1,3-thiazol-4-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(2-(1-piperidinyl)-1,3-thiazol-4-yl)phenyl)methyl)-1-phenylethanamine;

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- (1R)-1-phenyl-N-((6-((2,2,2-trifluoroethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 5 (1R)-N-((6-chloro-4'-(trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 10 1-(3,5-difluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 1-(3-bromophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 15 1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1S)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-(3-(2-chloropyrid-4-yl)-4-methoxyphenyl)methyl-N-1-phenylethylamine;
- 20 (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 25 (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

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- (1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 5 (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 10 (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-fluorophenyl)ethanamine;
- (1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-chloro-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-phenylethanamine;

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- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- N-1-(3-(dimethylamino)phenyl)ethyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)amine;
- 5 N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-((trifluoromethyl)oxy)phenyl)ethanamine;
- 5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-1-(2,2,2-trifluoroethyl)-2(1H)-pyridinone;
- 5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1-(2,2,2-trifluoroethyl)-2(1H)-pyridinone;
- 10 1-(4-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 1-(2,3-dichlorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 15 1-methyl-5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- 1-methyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((3-imidazo[1,2-a]pyridin-6-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;

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- (1R)-1-(1-naphthalenyl)-N-((6-((2,2,2-trifluoroethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 1-methyl-5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- 5 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-(1-piperidinyl)-1,3-thiazol-4-yl)phenyl)methyl)ethanamine;
- (1R)-N-((6-chloro-4'-(trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-chloro-4'-(trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;
- 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;
- 15 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-1-(1-naphthalenyl)-N-((3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-ol;
- (1R)-N-((3-imidazo[1,2-a]pyridin-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 30 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1-acetyl-4-piperidinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;



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- (1R)-N-((4-(methyloxy)-3-(1-((methyloxy)acetyl)-4-piperidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((2-(methyloxy)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 5 (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 10 (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-phenylethanamine;
- 15 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)ethanamine;
- ethyl 4-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3,6-dihydro-1(2H)-pyridinecarboxylate;
- (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 25 (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid;
- 30 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid;

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- 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid;
- (1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-phenylethanamine;
- 5 (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 10 (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 (1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine;



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- (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 5 (1R)-N-((3-(1-methyl-1H-benzimidazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-phenylethanamine;
- 10 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 15 (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 (1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;

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- (1R)-N-((3-(2-ethyl-2H-1,2,3-benzotriazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenyl-1-propanamine;
- 10 (1R)-N-((4-methyl-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(1-
- 15 naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-pyrimidinamine;
- 5-(2-(methyloxy)-5-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyrimidinamine;
- 5-(3-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-3-
- 25 pyridinecarboxamide;
- 5-(3-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
- 5-(3-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
- 30 (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;

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(1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;

(1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine; and

5 (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;

For the treatment of bone disorders, such as osteoporosis, excessive secretion of PTH, such as hyperparathyroidism, and the like, the compounds of the present invention may be administered orally, parentally, by inhalation spray,  
10 rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term "parenteral" as used herein includes, subcutaneous, intravenous, intramuscular, intrasternal, infusion techniques or intraperitoneally.

Treatment of diseases and disorders herein is intended to also include the  
15 prophylactic administration of a compound of the invention, a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (*i.e.*, an animal, preferably a mammal, most preferably a human) believed to be in need of preventative treatment, such as, for example, pain, inflammation and the like.

The dosage regimen for treating the disclosed diseases with the  
20 compounds of this invention and/or compositions of this invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. Dosage levels of  
25 the order from about 0.01 mg to 30 mg per kilogram of body weight per day, preferably from about 0.1 mg to 10 mg/kg, more preferably from about 0.25 mg to 1 mg/kg are useful for all methods of use disclosed herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal  
30 agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a capsule, a tablet, a suspension, or liquid. The

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pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily  
5 dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily  
10 parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable  
15 dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition,  
20 sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by  
25 mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily.  
30 For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may

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comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% w/w of the formulation.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments,  
5 lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch  
10 powder, cellulose esters of alkanolic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene  
15 glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

20 The pharmaceutical compositions may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents,  
25 emulsifiers, buffers etc.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional  
30 substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also

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comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert  
5 diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or  
10 more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

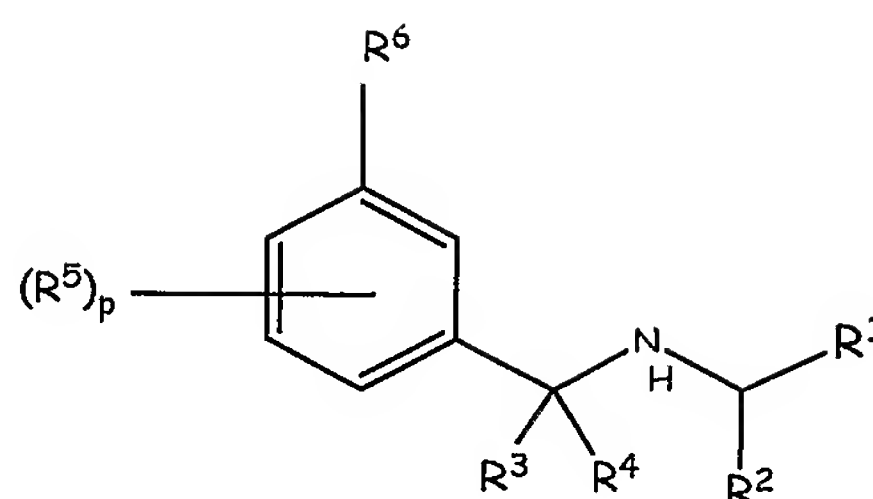
The foregoing is merely illustrative of the invention and is not intended to  
15 limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.



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## WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

$R^1$  is aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, or substituted cycloalkyl;

$R^2$  is alkyl or haloalkyl;

$R^3$  is H, alkyl, or haloalkyl;

$R^4$  is H, alkyl, or haloalkyl;

each  $R^5$  present is independently alkyl, substituted alkyl, alkoxy, substituted alkoxy, halogen,  $-C(=O)OH$ ,  $-CN$ ,  $-NR^dS(=O)_mR^d$ ,  $-NR^dC(=O)NR^dR^d$ ,  $-NR^dS(=O)_mNR^dR^d$ , or  $-NR^dC(=O)R^d$ ;

$R^6$  is aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, or substituted cycloalkyl;

each  $R^a$  is, independently, H, alkyl or haloalkyl;

each  $R^b$  is, independently, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl, each of which may be unsubstituted or substituted by up to 3 substituents selected from the group

consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

each  $R^c$  is, independently, alkyl, haloalkyl, phenyl or benzyl, each of which may be substituted or unsubstituted;

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each  $R^d$  is, independently, H, alkyl, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl wherein the alkyl, aryl, aralkyl, heterocyclyl, and heterocyclylalkyl are substituted by 0, 1, 2, 3 or 4 substituents selected from alkyl, halogen, haloalkyl, alkoxy, cyano, nitro,  $R^b$ ,  
 5  $-C(=O)R^c$ ,  $-OR^b$ ,  $-NR^aR^a$ ,  $-NR^aR^b$ ,  $-C(=O)OR^c$ ,  $-C(=O)NR^aR^a$ ,  
 $-OC(=O)R^c$ ,  $-NR^aC(=O)R^c$ ,  $-NR^aS(=O)_nR^c$  and  $-S(=O)_nNR^aR^a$ ;

m is 1 or 2;

n is 0, 1 or 2; and

p is 0, 1, 2, 3, or 4,

10 provided that if  $R^2$  is methyl, p is 0, and  $R^6$  is unsubstituted phenyl, then  $R^1$  is not 2,4-dihalophenyl, 2,4-dimethylphenyl, 2,4-diethylphenyl, 2,4,6-trihalophenyl, or 2,3,4-trihalophenyl.

2. A compound or salt of claim 1 wherein  $R^1$  is aryl or substituted aryl.
- 15 3. A compound or salt of claim 1 wherein  $R^1$  is phenyl, substituted phenyl, naphthyl, or substituted naphthyl.
4. A compound or salt of claim 1 wherein  $R^1$  is phenyl or substituted phenyl.
5. A compound or salt of claim 1 wherein  $R^1$  is phenyl that is unsubstituted or substituted by a substituent selected from the group consisting of  
 20 halogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, and cyano.
6. A compound or salt of claim 1 wherein  $R^1$  is phenyl substituted by a halogen, methyl, or methoxy group.
7. A compound or salt of claim 6 wherein the substituent is in the 3-position.
8. A compound or salt of claim 1 wherein  $R^1$  is heteroaryl or substituted  
 25 heteroaryl.
9. A compound or salt of claim 1 wherein  $R^6$  is heterocyclyl or substituted heterocyclyl.
10. A compound or salt of claim 1 wherein  $R^6$  is a 2-pyridyl or 3-pyridyl group that is substituted or unsubstituted.
- 30 11. A compound or salt of claim 1 wherein  $R^6$  is phenyl, substituted phenyl, naphthyl, or substituted naphthyl.
12. A compound or salt of claim 1 wherein  $R^6$  is phenyl or substituted phenyl.



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13. A compound or salt of claim 1 wherein  $R^6$  is phenyl that is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of  $C_{1-4}$ haloalkyl,  $C_{1-4}$ haloalkoxy,  $C_{1-4}$  alkoxy, methylenedioxy, cyano,  $C_{1-4}$  alkyl,  $-NH-C(=O)-C_{1-4}$  alkyl,  $-(CH_2)_{0-3}-C(=O)-NH_2$ ,  $-S(=O)_2-C_{1-4}$  alkyl,  $-(CH_2)_{0-3}-C(=O)O-C_{1-4}$  alkyl, and  $-(CH_2)_{0-3}-C(=O)-OH$ .
14. A compound or salt of claim 1 wherein  $R^6$  is phenyl that is unsubstituted or substituted by a halogen, methoxy, trifluoromethyl, or trifluoromethoxy group.
15. A compound or salt of claim 1 wherein  $R^6$  is a phenyl group that is substituted at the 4-position and may be further substituted.
16. A compound or salt of claim 1 wherein each  $R^5$  present is independently selected from the group consisting of halogen,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy,  $-NR^a-S(=O)_2-C_{1-4}$  alkyl,  $-NR^a-C(=O)-NR^a-C_{1-4}$  alkyl,  $-O-C_{1-4}$  alkylene- $C(=O)-NR^aR^a$ , and  $-O-C_{1-4}$  alkylene- $O-C_{1-4}$  alkyl.
17. A compound or salt of claim 1 wherein p is 0.
18. A compound or salt of claim 1 wherein p is 1 and  $R^5$  is methoxy.
19. A compound or salt of claim 18 wherein  $R^5$  is in the 4-position.
20. A compound or salt of claim 19 wherein  $R^1$  is phenyl, substituted phenyl, or naphthyl.
21. A compound or salt of claim 19 wherein  $R^6$  is phenyl or substituted phenyl.
22. A compound or salt of claim 19 wherein  $R^6$  is phenyl that is unsubstituted or substituted by a halogen, methoxy, trifluoromethyl, or trifluoromethoxy group.
23. A compound or salt of claim 22 wherein  $R^1$  is phenyl, 1-naphthyl, or 2-naphthyl that is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of halogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, and cyano.
24. A compound or salt of claim 22 wherein  $R^1$  is phenyl substituted by 1 or 2 substituents selected from the group consisting of halogen, methyl, methoxy, and cyano.
25. A compound or salt of claim 1 wherein  $R^2$  is methyl.
26. A compound or salt of claim 23 wherein  $R^2$  is methyl.

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27. A compound or salt of claim 1 wherein R<sup>3</sup> and R<sup>4</sup> are both hydrogen.
28. A compound or salt of claim 26 wherein R<sup>3</sup> and R<sup>4</sup> are both hydrogen.
29. A compound selected from the group consisting of:
  - (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
  - (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
  - (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
  - (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
  - (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
  - (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
  - (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
  - (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
  - (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
  - (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine;
  - (1R)-N-((3-(1-methyl-1H-benzimidazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
  - (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
  - (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
  - (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
  - (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
  - (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
  - (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
  - (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
  - (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-phenylethanamine;
  - (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine;
  - ethyl 4-(2-(methyloxy)-5-(((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3,6-dihydro-1(2H)-pyridinecarboxylate;

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- (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 10 (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 15 (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)-1-phenylethanamine;
- 20 (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 (1R)-N-((4-chloro-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 30 (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 35 (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-fluorophenyl)ethanamine;
- (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 40 (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 45 (1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;

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- 1-(3-bromophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;  
1-(3,5-difluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;  
5 (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((6-chloro-4'-(trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
10 (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;  
15 (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;  
20 (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
25 ethyl 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;  
ethyl 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;  
4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1,3-thiazol-2-amine;  
30 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
35 (1R)-N-((4-(methyloxy)-3-(2-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(2-fluoro-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
40 N,N-dimethyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine;  
(1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-phenylethanamine;  
45 (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-phenylethanamine;



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- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)ethanamine;  
 5 (1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-N-((4-(methyloxy)-3-(2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 10 (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;  
 15 (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;  
 20 (1R)-N-((6-(ethyloxy)-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
 (1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 25 (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine; and  
 (1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine  
 30 or a pharmaceutically acceptable salt thereof.
30. A compound selected from the group consisting of:
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine;  
 35 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;  
 (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;  
 (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;  
 40 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
 (1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-N-((4-(methyloxy)-3-(6-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;  
 45 (1R)-N-((4-(methyloxy)-3-(2-(4-morpholinyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;

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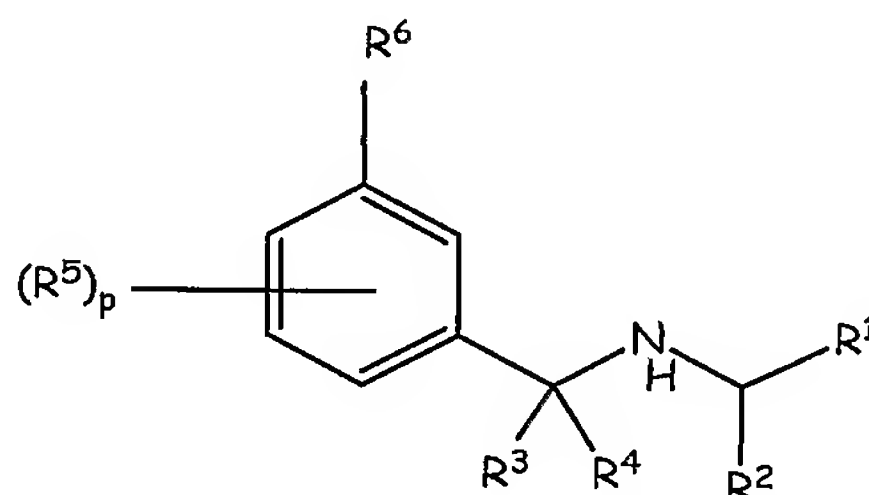
(1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-phenylethanamine;  
5 ethyl 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;  
N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-methylphenyl)ethanamine;  
(1R)-N-((6-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
10 N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;  
N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;  
15 N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;  
(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
(1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;  
20 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;  
(1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
25 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;  
30 (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;  
35 (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
(1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
40 (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-phenylethanamine;  
(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;  
45 (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;  
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)ethanamine;

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2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-  
 biphenyl-3-carboxamide;  
 (1R)-1-(1-naphthalenyl)-N-((3-(6-(trifluoromethyl)-3-  
 pyridinyl)phenyl)methyl)ethanamine;  
 5 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-  
 phenylethanamine;  
 (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-  
 (1-naphthalenyl)ethanamine;  
 (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-  
 10 (3-(methyloxy)phenyl)ethanamine;  
 (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-  
 naphthalenyl)ethanamine;  
 (1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-  
 (1-naphthalenyl)ethanamine;  
 15 (1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-  
 yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;  
 (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(3-  
 (methyloxy)phenyl)ethanamine;  
 (1R)-N-((3-(2-ethyl-2H-1,2,3-benzotriazol-5-yl)-4-  
 20 (methyloxy)phenyl)methyl)-1-phenylethanamine; and  
 (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-  
 (methyloxy)phenyl)ethanamine

or a pharmaceutically acceptable salt thereof.

31. A composition comprising a pharmaceutically acceptable amount of a  
 compound of the formula Ia:



(Ia)

or a pharmaceutically acceptable salt thereof,

wherein:

**R<sup>1</sup>** is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl,  
 35 or substituted heterocyclyl;

**R<sup>2</sup>** is alkyl or haloalkyl;

**R<sup>3</sup>** is H, alkyl, or haloalkyl;

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$R^4$  is H, alkyl, or haloalkyl;

each  $R^5$  present is independently alkyl, substituted alkyl, haloalkyl, alkoxy, substituted alkoxy, halogen,  $-C(=O)OH$ ,  $-CN$ ,  $-NR^aR^d$ ,  $-NR^dS(=O)_mR^d$ ,  $-NR^dC(=O)NR^dR^d$ ,  $-NR^dS(=O)_mNR^dR^d$ , or  $-NR^dC(=O)R^d$ ;

$R^6$  is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, or substituted heterocyclyl;

each  $R^a$  is, independently, H, alkyl or haloalkyl;

each  $R^b$  is, independently, aryl, aralkyl, heterocyclyl, or heteroaryl, each of which may be unsubstituted or substituted by up to 3 substituents selected from the group consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

each  $R^c$  is, independently, alkyl, haloalkyl, phenyl or benzyl;

each  $R^d$  is, independently, H, alkyl, aryl, aralkyl, or heterocyclyl, wherein the alkyl, aryl, aralkyl, and heterocycle are substituted by 0, 1, 2, 3 or 4 substituents selected from alkyl, halogen, haloalkyl, alkoxy, cyano, nitro,  $R^b$ ,  $-C(=O)R^c$ ,  $-OR^b$ ,  $-NR^aR^a$ ,  $-NR^aR^b$ ,  $-C(=O)OR^c$ ,  $-C(=O)NR^aR^a$ ,  $-OC(=O)R^c$ ,  $-NR^aC(=O)R^c$ ,  $-NR^aS(=O)_nR^c$  and  $-S(=O)_nNR^aR^a$ ;

$m$  is 1 or 2;

$n$  is 0, 1 or 2; and

$p$  is 0, 1, 2, 3, or 4, in combination with a pharmaceutically acceptable carrier.

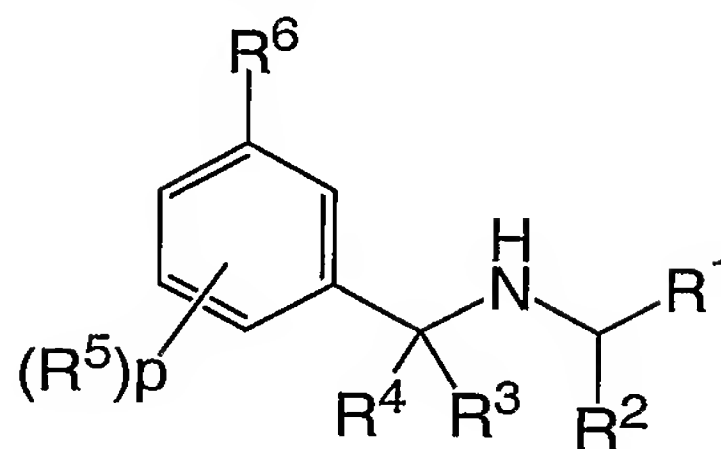
32. A method of treating a disease associated with excessive secretion of PTH comprising administering a therapeutically effective amount of a composition of claim 31 to a patient in need thereof.

33. A method of treating osteoporosis or hyperparathyroidism comprising administering a therapeutically effective amount of a composition of claim 31 to a patient in need thereof.



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34. A compound having the formula



or a pharmaceutically acceptable salt thereof, wherein:

- $R^1$  is phenyl, benzyl, naphthyl or a saturated or unsaturated 5- or  
 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N,  
 O and S, with no more than 2 of the atoms selected from O and S, wherein  
 the phenyl, benzyl, naphthyl or heterocycle are substituted by 0, 1, 2 or 3  
 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  
 cyano and nitro;
- $R^2$  is  $C_{1-8}$ alkyl or  $C_{1-4}$ haloalkyl;
- $R^3$  is H,  $C_{1-4}$ haloalkyl or  $C_{1-8}$ alkyl;
- $R^4$  is H,  $C_{1-4}$ haloalkyl or  $C_{1-8}$ alkyl;
- $R^5$  is, independently, in each instance, H,  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halogen,  
 cyano,  $-NR^aR^d$ ,  $-NS(=O)_2R^c$ ,  $-NR^aC(=O)NR^aR^d$ ,  $-NR^dC(=O)R^d$  or  
 $-OC_{1-6}$ alkyl substituted by 0, 1, 2 or 3 substituents selected from halogen,  
 $-OC_{1-6}$ alkyl,  $-NR^aR^d$ ,  $-NS(=O)_2R^c$ ,  $-NR^aC(=O)NR^aR^d$ ,  $-NR^dC(=O)R^d$  or  
 cyano;
- $R^6$  is phenyl, benzyl, naphthyl, a saturated or unsaturated 5- or  
 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N,  
 O and S, with no more than 2 of the atoms selected from O and S, or a  
 saturated or unsaturated 8-, 9-, 10- or 11-membered heterobicycle  
 containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more  
 than 2 of the atoms selected from O and S, wherein the phenyl, benzyl,  
 naphthyl, heterocycle and heterobicycle are substituted by 0, 1, 2 or 3  
 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  
 $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano  
 and nitro;
- $R^a$  is, independently, at each instance, H,  $C_{1-4}$ haloalkyl or  $C_{1-6}$ alkyl;

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$R^b$  is, independently, aryl, aralkyl, heterocyclyl, or heterocyclalkyl, each of which may be unsubstituted or substituted by up to 3 substituents selected from the group consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

5  $R^c$  is, independently, at each instance,  $C_{1-6}$ alkyl,  $C_{1-4}$ haloalkyl, phenyl or benzyl, each of which may be unsubstituted or substituted;

10  $R^d$  is, independently, at each instance, H,  $C_{1-6}$ alkyl, phenyl, benzyl or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the  $C_{1-6}$ alkyl, phenyl, benzyl, naphthyl and heterocycle are substituted by 0, 1, 2, 3 or 4 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro,  $R^b$ ,  $-C(=O)R^c$ ,  $-OR^b$ ,  $-NR^aR^a$ ,  $-NR^aR^b$ ,  $-C(=O)OR^c$ ,  $-C(=O)NR^aR^a$ ,  $-OC(=O)R^c$ ,  $-NR^aC(=O)R^c$ ,  $-NR^aS(=O)_mR^c$  and  $-S(=O)_mNR^aR^a$ ;

15 m is 1 or 2; and

n is 0, 1 or 2.

35. A compound according to claim 34 wherein  $R^1$  is phenyl, naphthyl or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl, naphthyl or heterocycle are substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro and  $R^6$  is phenyl, naphthyl, a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, or a saturated or unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl, naphthyl, heterocycle and heterobicycle are substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.

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36. A compound according to Claim 34, wherein  $R^1$  is phenyl substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.
- 5 37. A compound according to Claim 34, wherein  $R^1$  is benzyl substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.
- 10 38. A compound according to Claim 34, wherein  $R^1$  is naphthyl substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.
- 15 39. A compound according to Claim 34, wherein  $R^1$  a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.
- 20 40. A compound according to Claim 34, wherein  $R^6$  is phenyl, wherein the phenyl is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.
- 25 41. A compound according to Claim 34, wherein  $R^6$  is benzyl, wherein the benzyl is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.
- 30 42. A compound according to Claim 34, wherein  $R^6$  is naphthyl, wherein the naphthyl is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl,

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halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>,  
-NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.

43. A compound according to Claim 34, wherein R<sup>6</sup> is a saturated or  
5 unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms  
selected from N, O and S, with no more than 2 of the atoms selected from  
O and S, wherein the heterocycle is substituted by 0, 1, 2 or 3 substituents  
selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl,  
-OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano  
10 and nitro.
44. A compound according to Claim 34, wherein R<sup>6</sup> is a saturated or  
unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4  
or 5 atoms selected from N, O and S, with no more than 2 of the atoms  
15 selected from O and S, wherein the heterobicycle is substituted by 0, 1, 2  
or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl,  
-OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>  
C<sub>1-6</sub>alkyl, cyano and nitro.
- 20 45. A compound according to Claim 34, wherein R<sup>1</sup> is phenyl, naphthyl or  
(OC<sub>1-4</sub>alkyl)phenyl.
46. A compound according to Claim 34, wherein R<sup>1</sup> is phenyl substituted by 2  
or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl,  
25 -OC<sub>1-6</sub>alkyl, cyano and nitro.
47. A compound according to Claim 34, wherein R<sup>1</sup> is benzyl substituted by 1,  
2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl,  
-OC<sub>1-6</sub>alkyl, cyano and nitro.

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48. A compound according to Claim 34, wherein  $R^1$  is naphthyl substituted by 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.
- 5 49. A compound according to Claim 34, wherein  $R^1$  is a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl, cyano and nitro.
- 10 50. A compound according to Claim 34, wherein one of  $R^3$  or  $R^4$  is  $C_{1-4}$ haloalkyl or  $C_{1-8}$ alkyl.
- 15 51. A compound according to Claim 34, wherein  $R^5$  is  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halogen or  $-OC_{1-6}$ alkyl.
- 20 52. A compound according to Claim 34, wherein  $R^6$  is phenyl, wherein the phenyl is substituted by 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.
- 25 53. A compound according to Claim 34, wherein  $R^6$  is benzyl, wherein the benzyl is substituted by 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.
- 30 54. A compound according to Claim 34, wherein  $R^6$  is naphthyl, wherein the naphthyl is substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl, halogen,  $C_{1-4}$ haloalkyl,  $-OC_{1-6}$ alkyl,  $-OC_{1-4}$ haloalkyl,  $-NR^aR^a$ ,  $-NR^aC(=O)C_{1-6}$ alkyl,  $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.

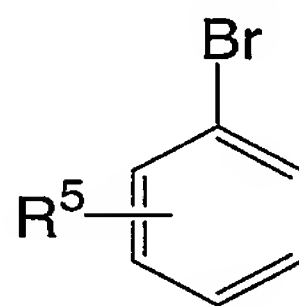
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55. A compound according to Claim 34, wherein R<sup>6</sup> is a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 1, 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.
56. A compound according to Claim 34, wherein R<sup>6</sup> is a saturated or unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterobicycle is substituted by 1, 2 or 3 substituents selected from C<sub>1-6</sub>alkyl, halogen, C<sub>1-4</sub>haloalkyl, -OC<sub>1-6</sub>alkyl, -OC<sub>1-4</sub>haloalkyl, -NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(=O)C<sub>1-6</sub>alkyl, -S(=O)<sub>n</sub>C<sub>1-6</sub>alkyl, cyano and nitro.
57. A pharmaceutical composition comprising a compound according to Claim 34 and a pharmaceutically acceptable diluent or carrier.
58. The use of a compound according to Claim 34 as a medicament.
59. The use of a compound according to Claim 34 in the manufacture of a medicament for the treatment of diseases associated with bone disorders or associated with excessive secretion of PTH.
60. The use of a compound according to Claim 34 in the manufacture of a medicament for the treatment of osteoporosis or hyperparathyroidism.
61. A method of using a compound according to Claim 34 for the treatment of diseases associated with bone disorders or associated with excessive secretion of PTH.

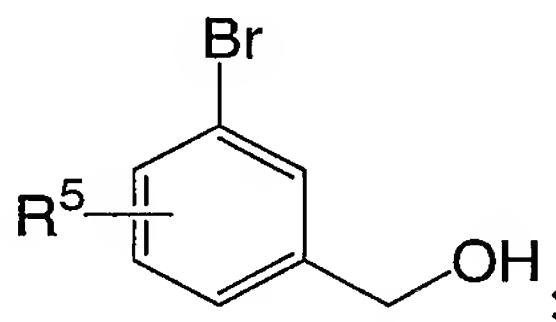
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62. A method of using a compound according to Claim 34 for the treatment of osteoporosis or hyperparathyroidism.

63. A process for making a compound according to Claim 1, wherein  $R^3$  and  $R^4$  are both H comprising the steps of:  
5 placing a compound having the structure

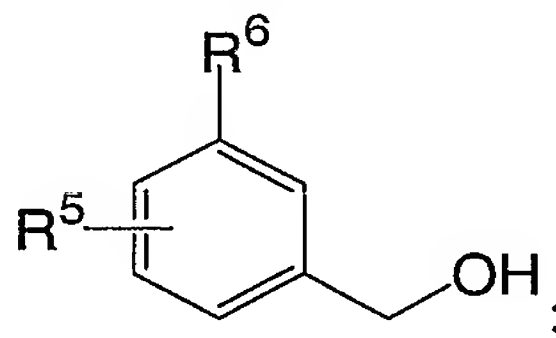


in the presence of acid followed by treatment with a hydride and methanol to form

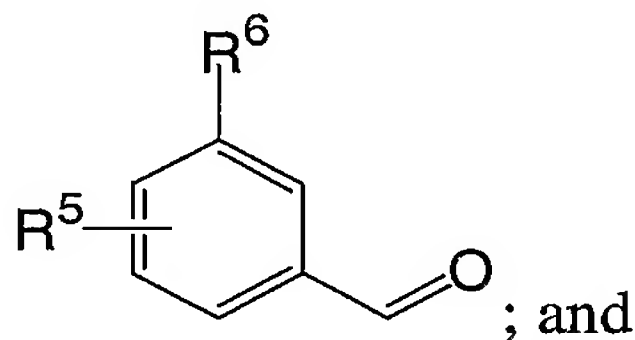


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reacting the resulting alcohol with  $R^6$ -B(OH)<sub>2</sub> to form

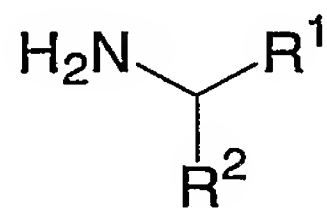


oxidizing the alcohol to form



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reacting the aldehyde with an amine having the structure





# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/16401

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C07C317/32 C07C311/08 C07C275/40 C07C255/59 C07C233/43 C07C233/18 C07C229/38 C07C217/58 C07C211/29 C07C211/27 C07C321/28 C07D213/38 C07D213/64 C07D263/56 C07D209/08					
According to International Patent Classification (IPC) or to both national classification and IPC					
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C C07D					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data					
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
X	WO 99 48888 A (SQUIBB BRISTOL MYERS CO) 30 September 1999 (1999-09-30)  page 22; example 26; table 1 ---				1-5, 9, 17, 23, 25-28, 34-36, 43, 45, 55, 57, 58
X	WO 03 020723 A (ENOKIZONO JUNICHI ;HAGIHARA KOJI (JP); SUZUKI KOJI (JP); ARAI HITO) 13 March 2003 (2003-03-13)  page 94; example 732; tables --- -/--				1-5, 9, 17, 23, 25-28, 34-36, 43, 45, 55, 57, 58
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.					
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family					
Date of the actual completion of the international search			Date of mailing of the international search report		
12 September 2003			22/09/2003		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016			Authorized officer  Bedel, C		



# INTERNATIONAL SEARCH REPORT

International Application No  
PC1/US 03/16401

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D277/28 C07D213/74 C07D211/26 C07D235/14 C07D239/26  
A61K31/167 A61K31/137 A61K31/4418 A61K31/423 A61K31/404  
A61K31/505 A61K31/445 A61K31/426 A61P3/14 A61P5/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

12 September 2003

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/16401

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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International Application No

PCT/US 03/16401

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Inte al Application No

PCT/US 03/16401

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